

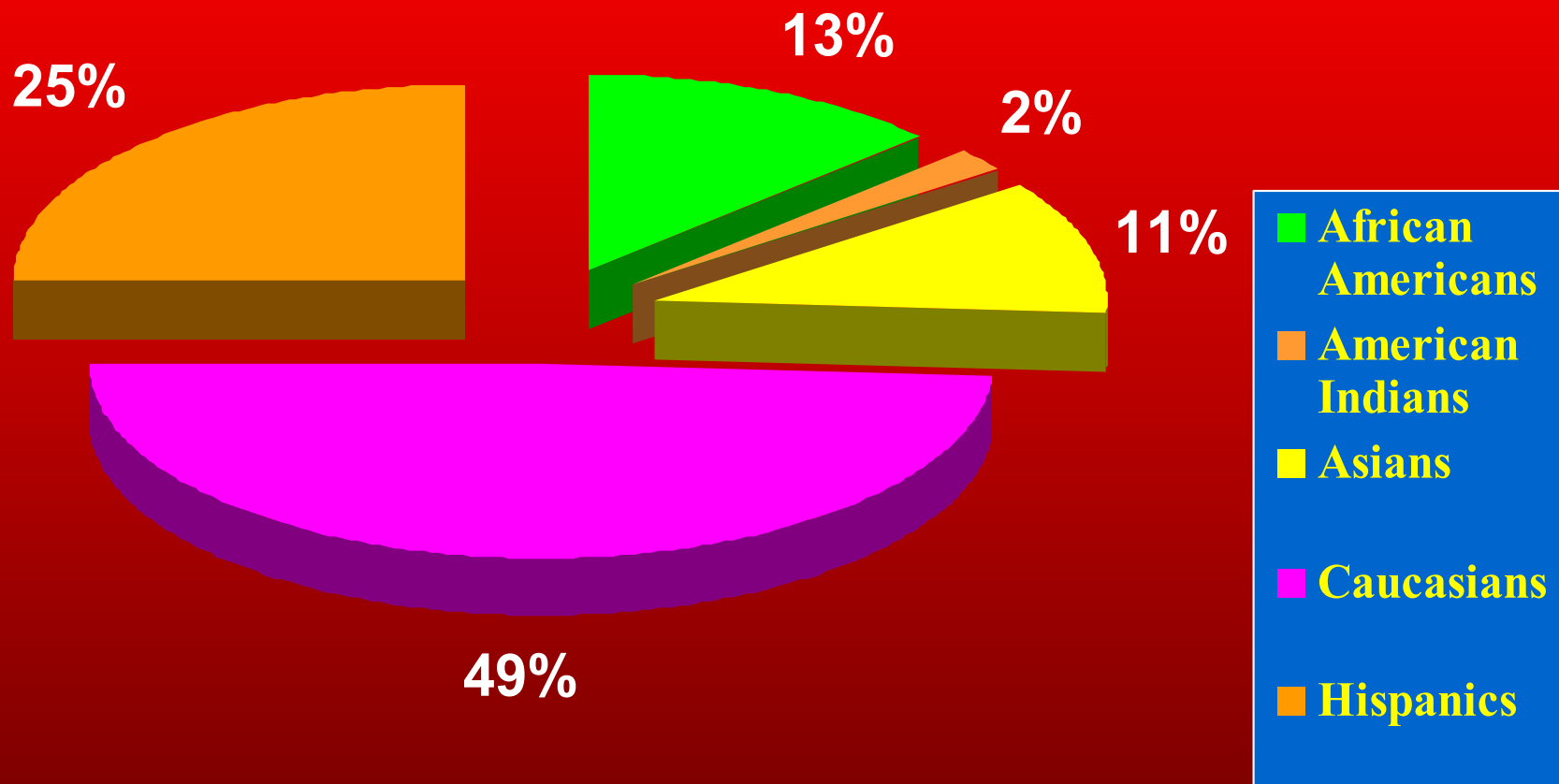
# ETHNICITY, CULTURE AND PHARMACOGENETICS

**Bridging Cultures & Enhancing  
Minority Healthcare in the New  
Millennium**

**January 25, 2003**

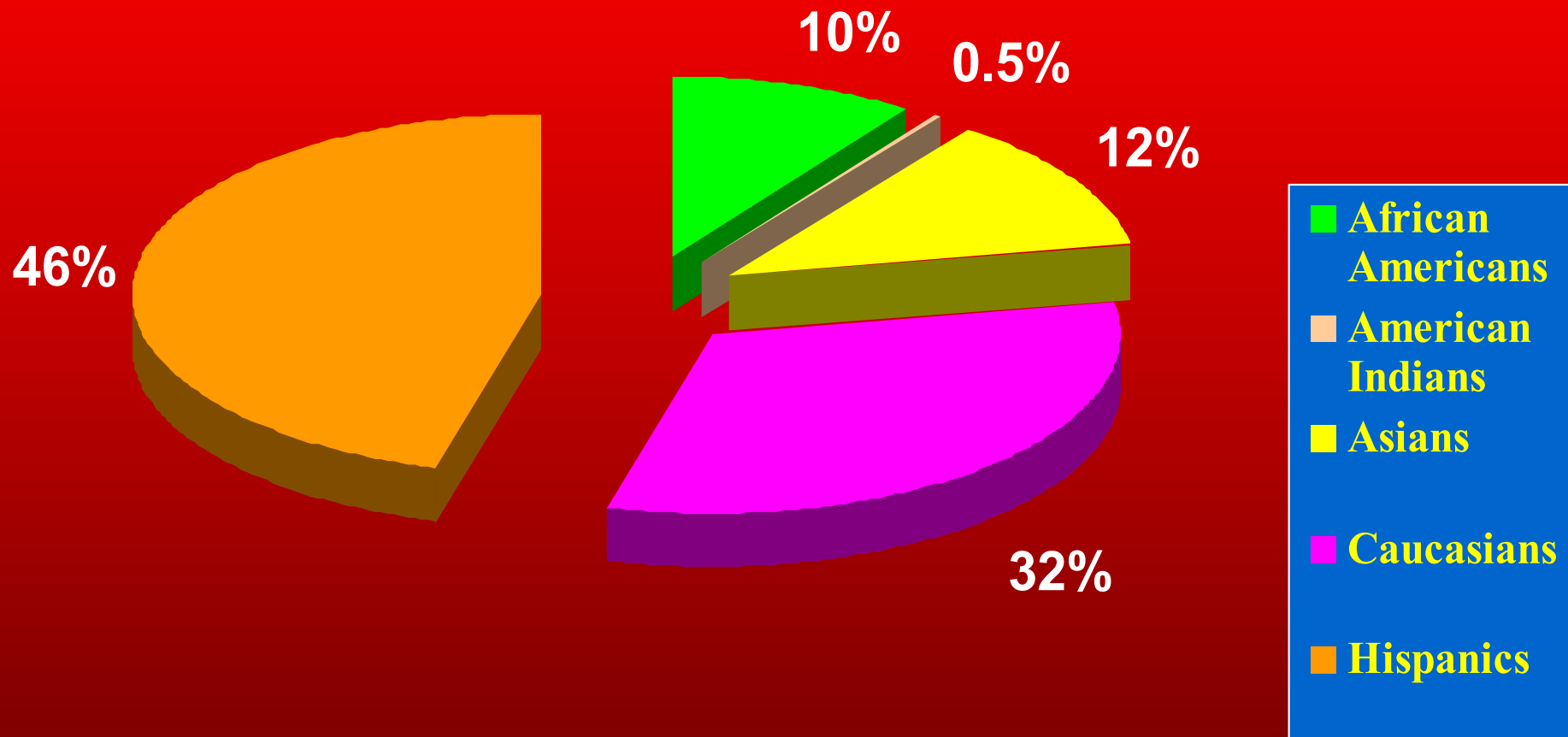
Keh-Ming Lin, M.D., M.P.H.  
Harbor-UCLA Medical Center  
Torrance CA

# POPULATION DISTRIBUTION USA (2050)

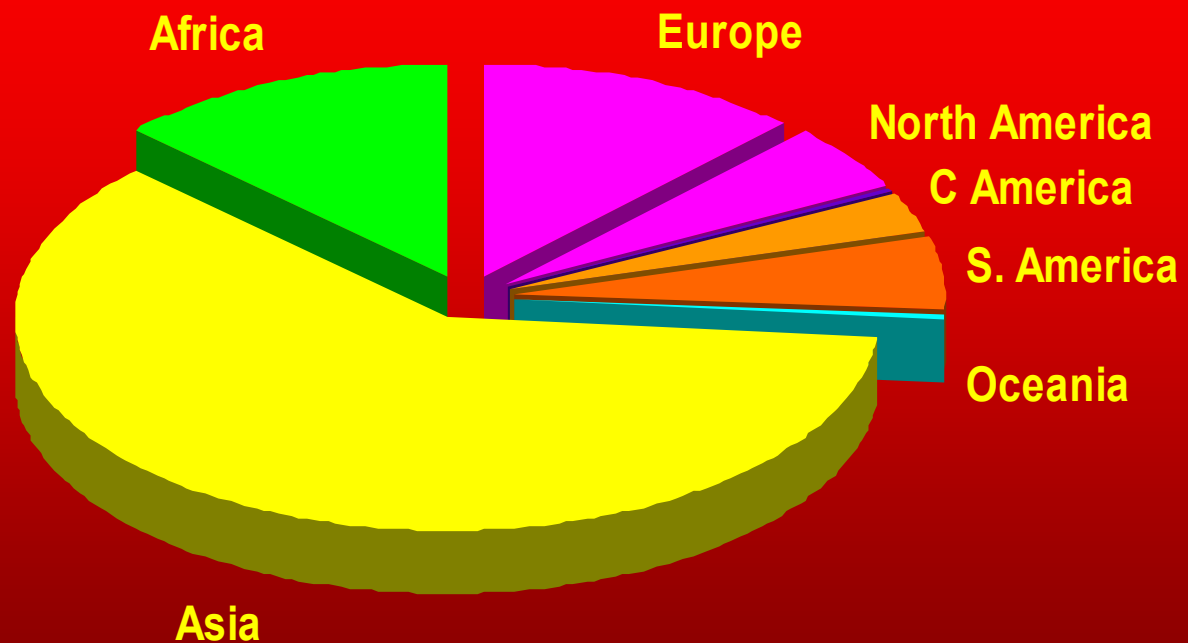


# POPULATION DISTRIBUTION

## Los Angeles County (2000)

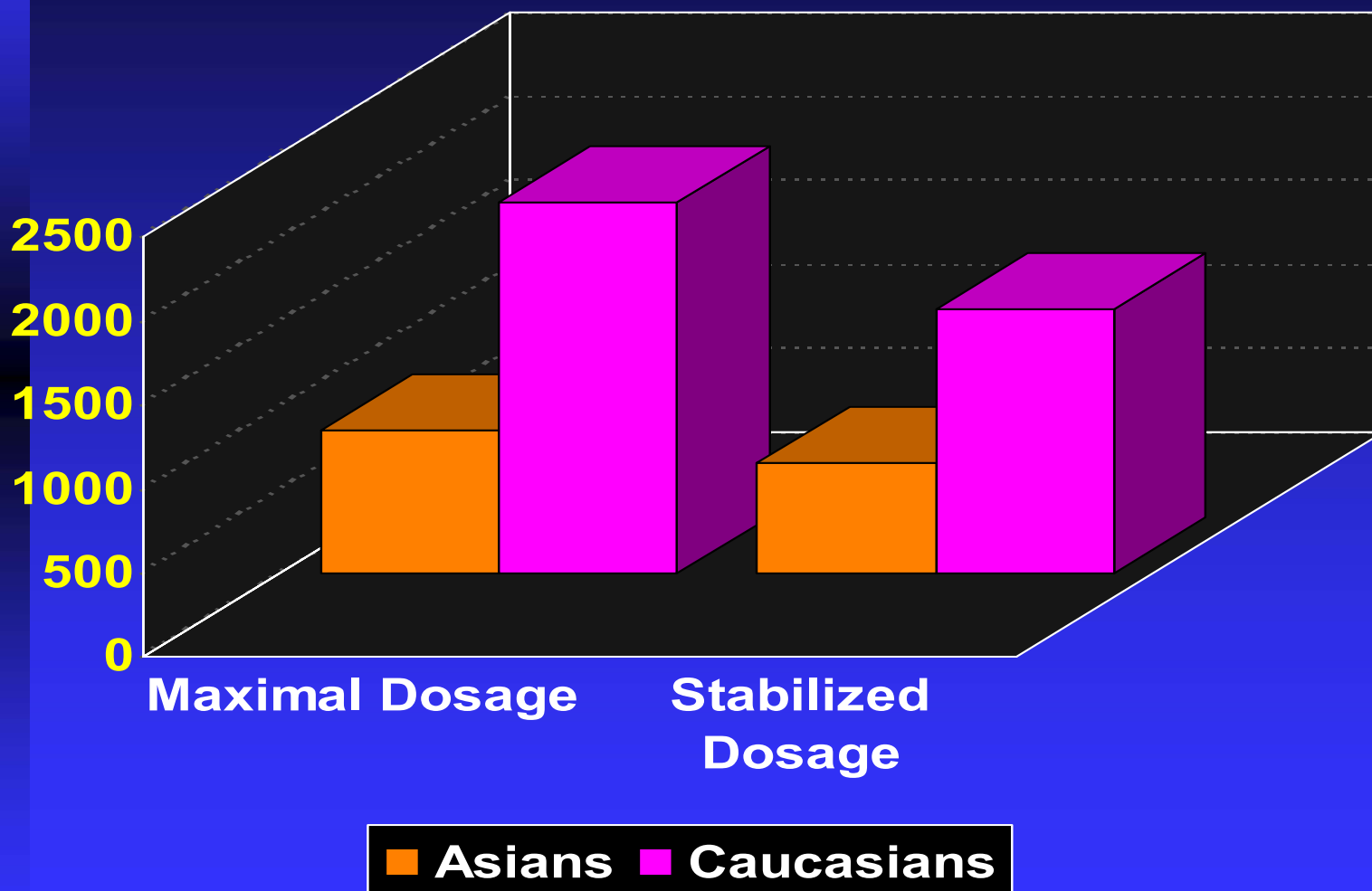


# THE POPULATION OF THE WORLD

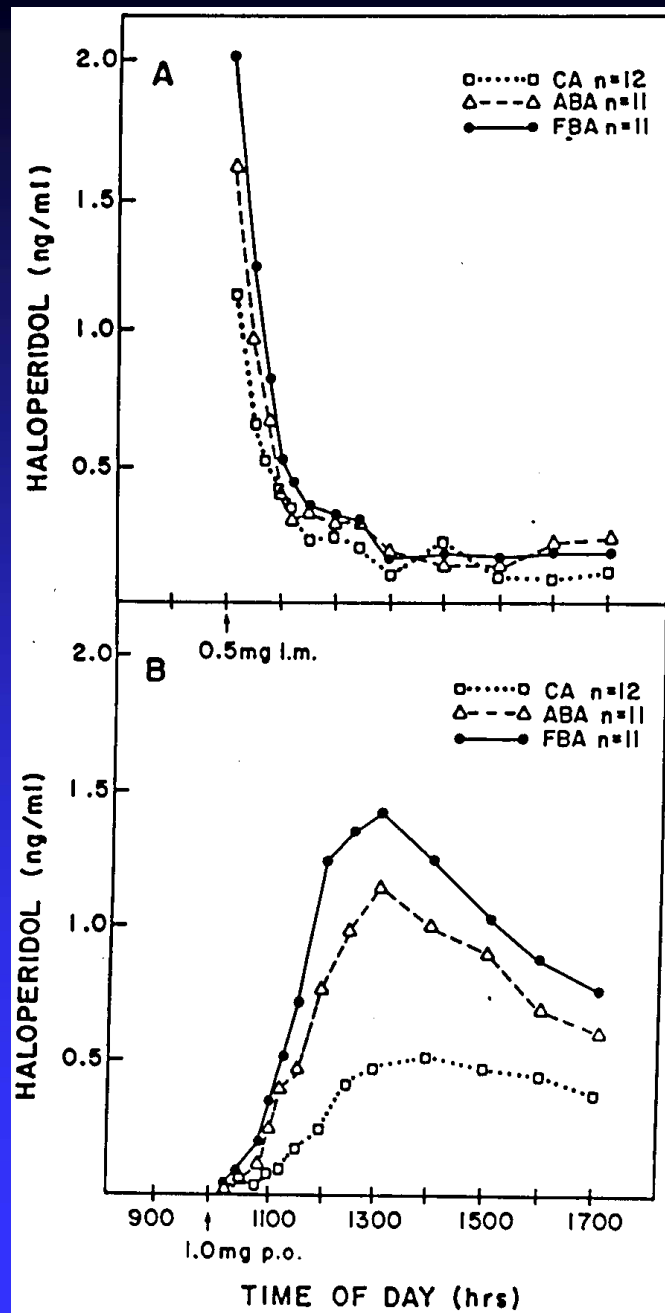


**One Size Does Not Fit All**

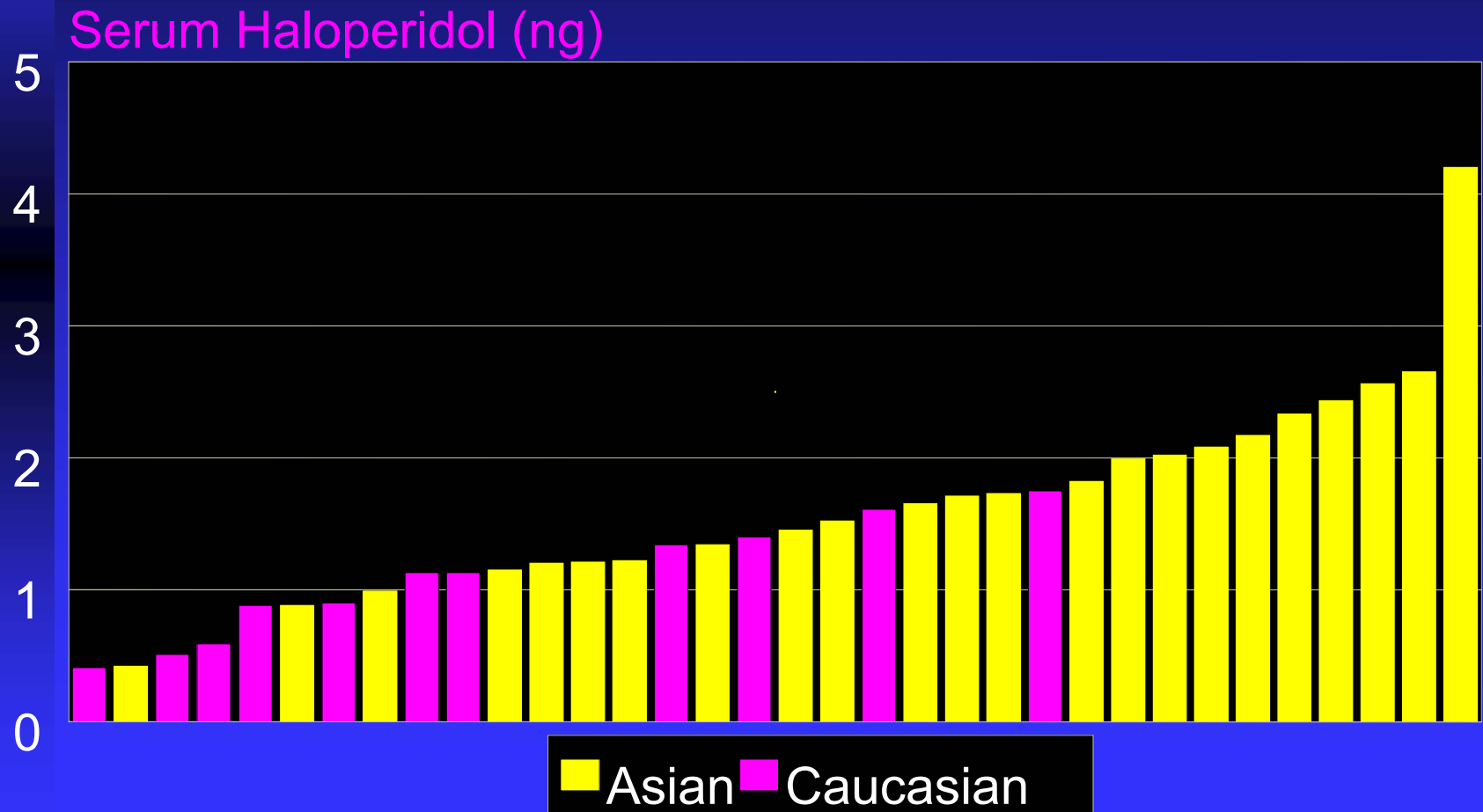
# NEUROLEPTIC DOSAGE FOR HOSPITALIZED PATIENTS: ASIANS VS CAUCASIANS



Lin & Finder, Am J Psychiatry 140:490-491, 1983

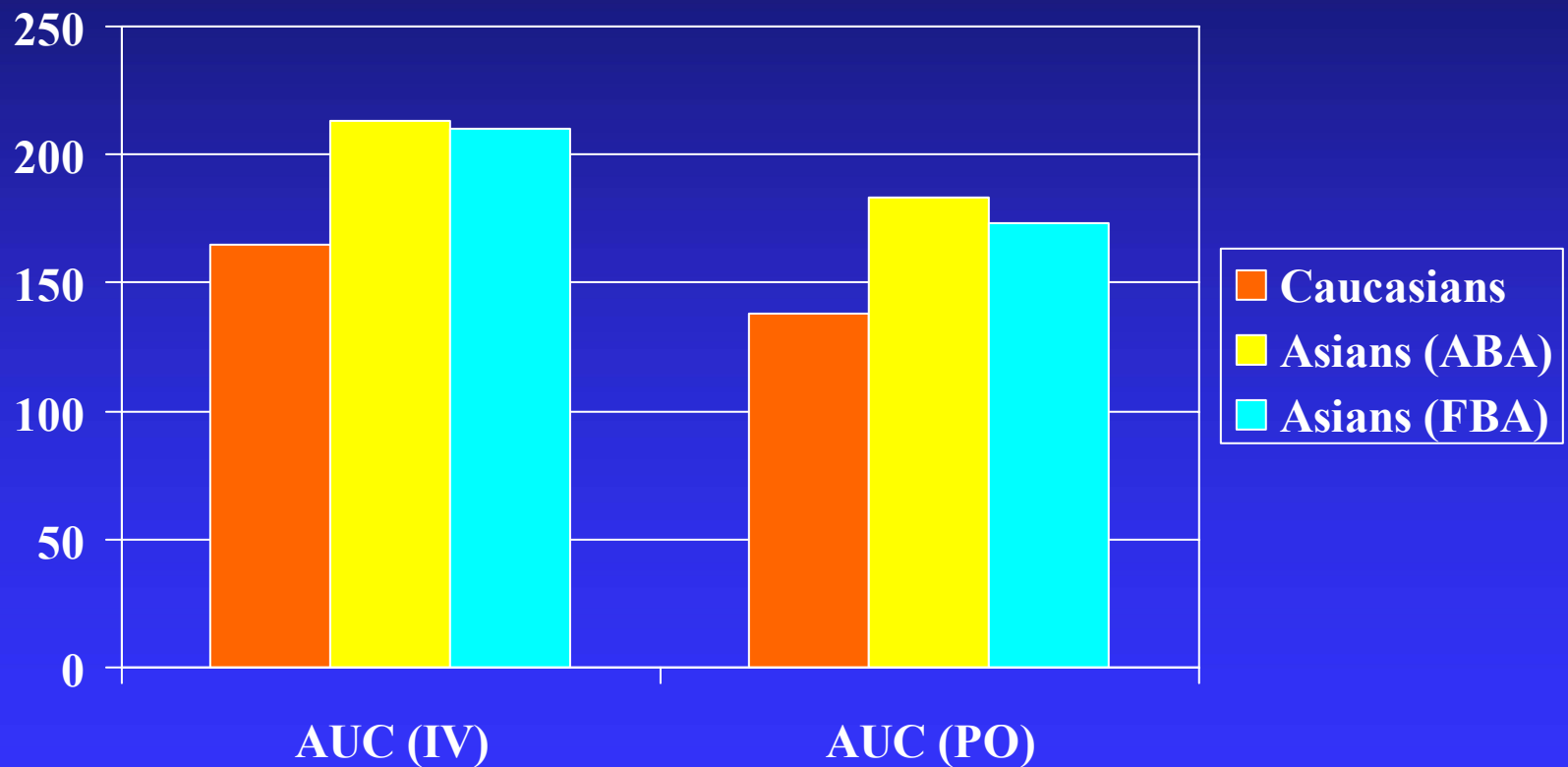


# Maximal Haloperidol Concentration After 0.5 mg i.m. Haloperidol





# Alprazolam Plasma Levels: Caucasian & Asian Volunteers



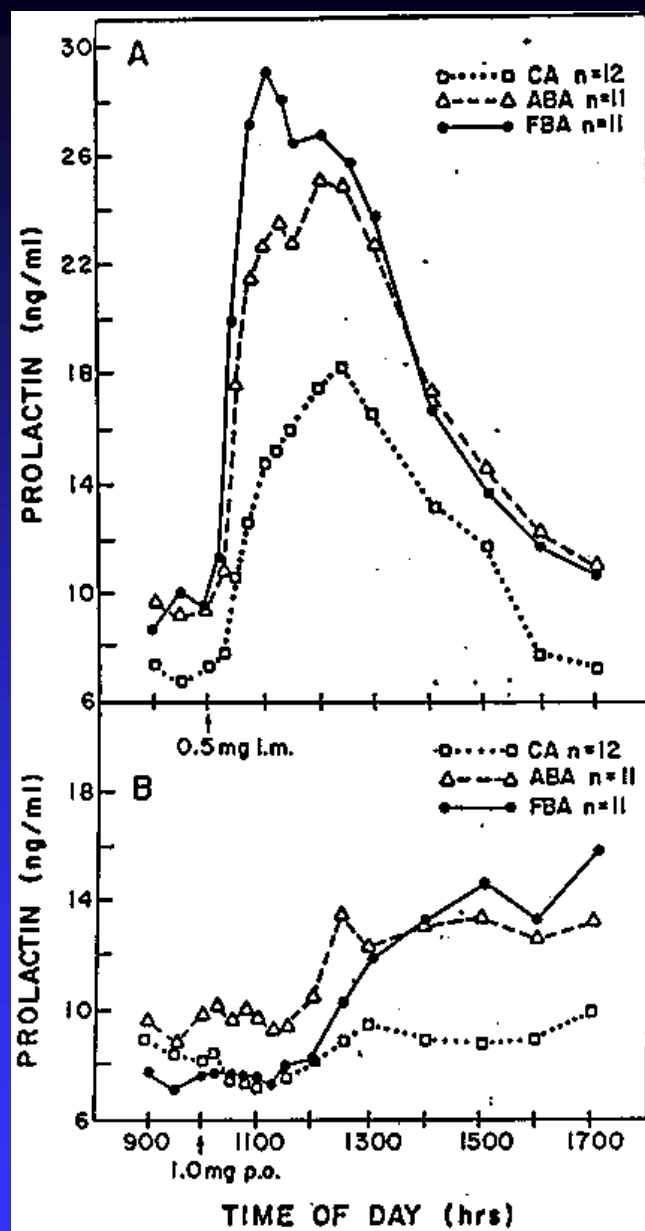
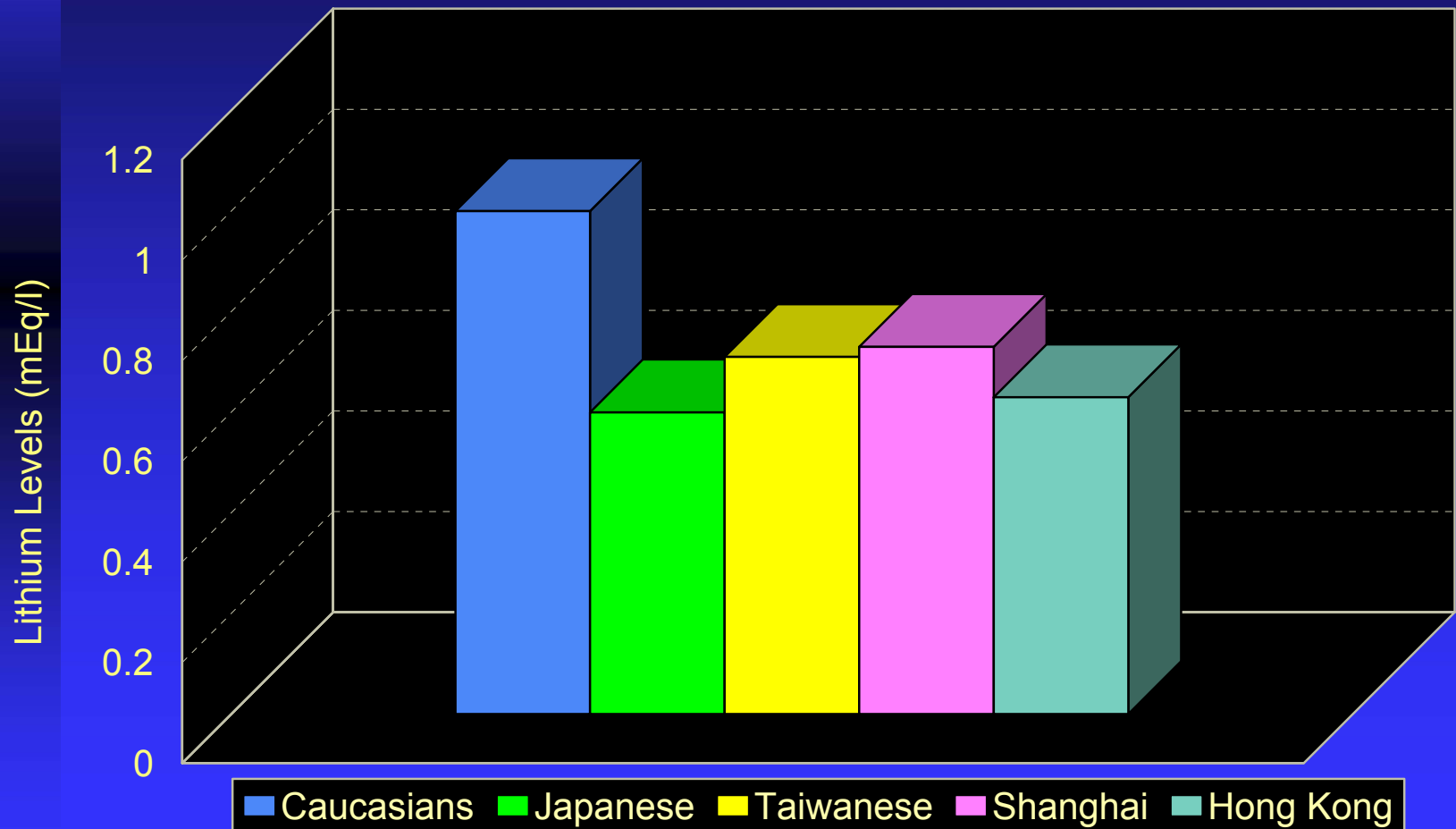
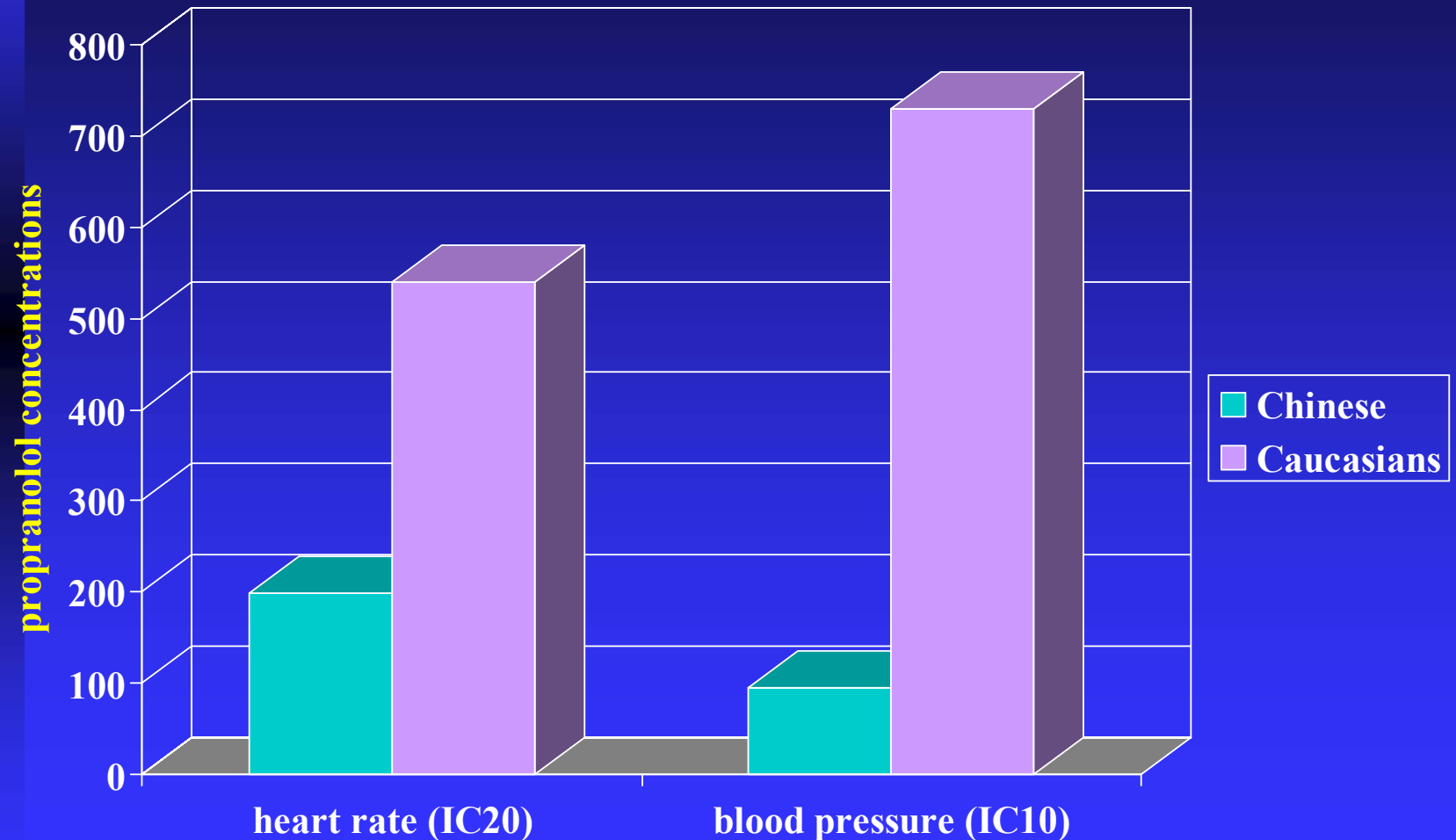


Figure 2. Mean serum prolactin concentrations the three comparison groups after (A) i.m. and (B) p.o. administration of haloperidol.

# Therapeutic Lithium Concentrations

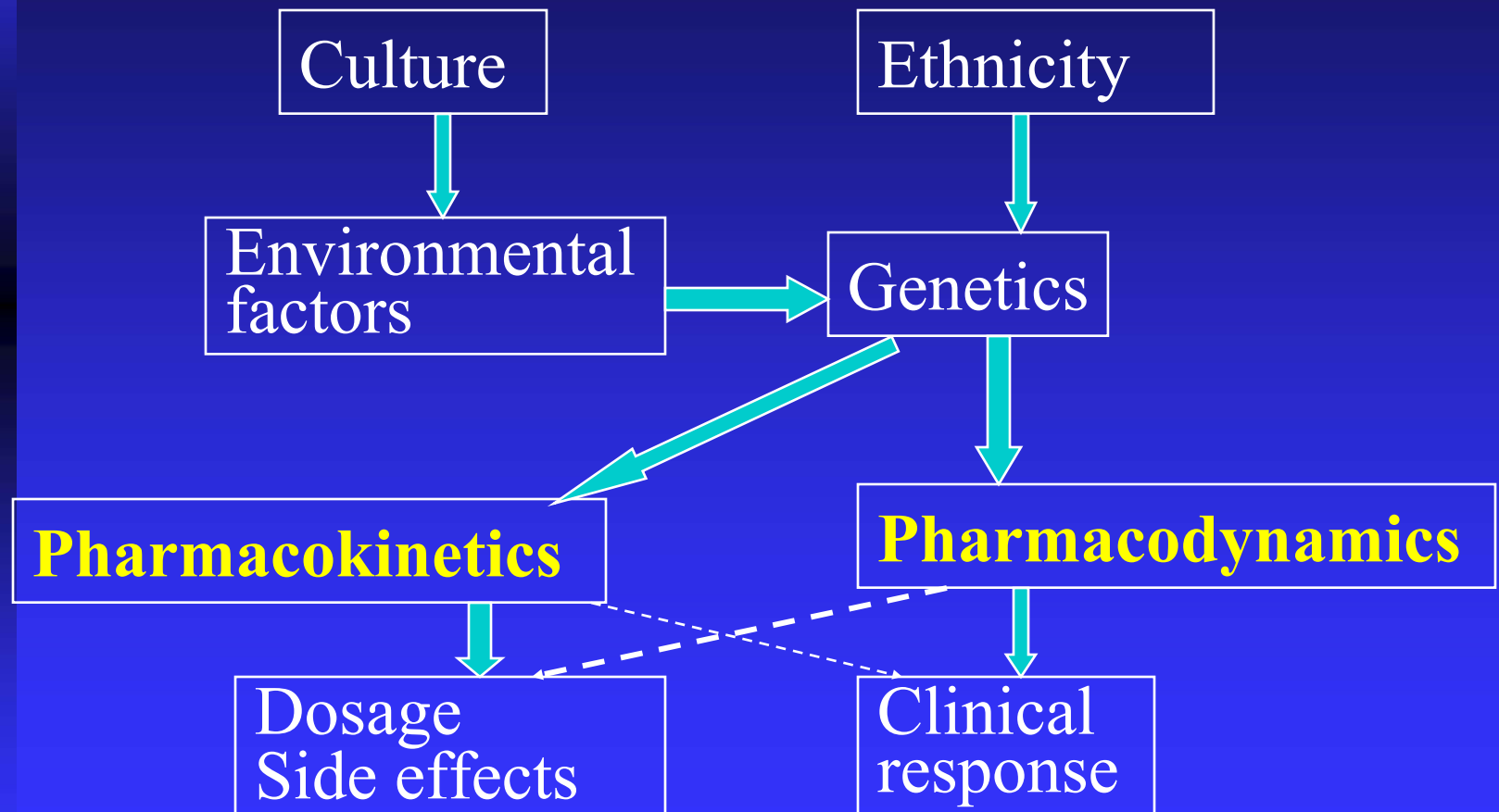


# Propranolol Response: Chinese vs Caucasians

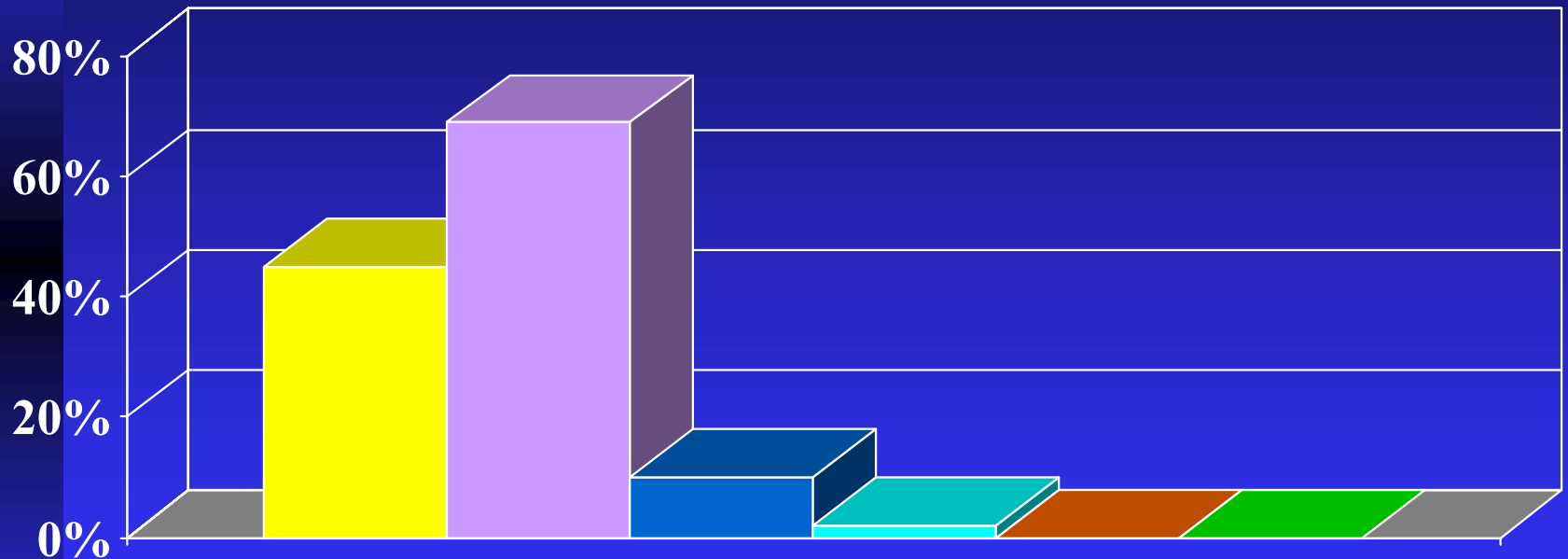


Zhou et al., NEJM 320:565-70, 1989

# Factors Determining Pharmacological Response



# PREVALENCE OF ACETALDEHYDE DEHYDROGENASE (ALDH) DEFICIENCY BY ETHNICITY



# CYTOCHROME P450 ENZYMES

- More than 50 expressed in humans
- The most important ones for drug metabolism are: CYP1A2, CYP2C19, CYP2D6, CYP2E1 and CYP3A4
- Variations in CYP2D6 largely determined by genetic factors
- Variations in CYP3A4 often influenced by environmental (dietary) factors

# Cytochrome P450 Enzymes and Neuroleptics

	CYP1A2	CYP2D6	CYP3A4
Haloperidol	++	++	--
Phenothiazines	+	++	--
Clozapine	++	+	++
Olanzapine	+++	++	--
Risperidone	--	+++	+
Quetiapine	--	--	+++
ziprasidone	--	--	+++



# Cytochrome P450 Enzymes and Antidepressants

	CYP1A2	CYP2C19	CYP2D6	CYP3A4
<b>TCAs (tertiary)</b>	++	+	++	++
<b>Fluoxetine</b>	+	++	++++	++
<b>Paroxetine</b>	+	-	++++	+
<b>Sertraline</b>	+	++	+	++
<b>Mirtazapine</b>	+	-	+	+
<b>Nefazodone</b>	+	-	+	++++
<b>Venlafaxine</b>	+	+	+	+
<b>Bupropion</b>	+	+	+	-
<b>Fluvoxamine</b>	++++	++	+	-
<b>TCAs (secondary)</b>	-	-	++	+

# Distribution of CYP2D6 Activity in Caucasian Populations

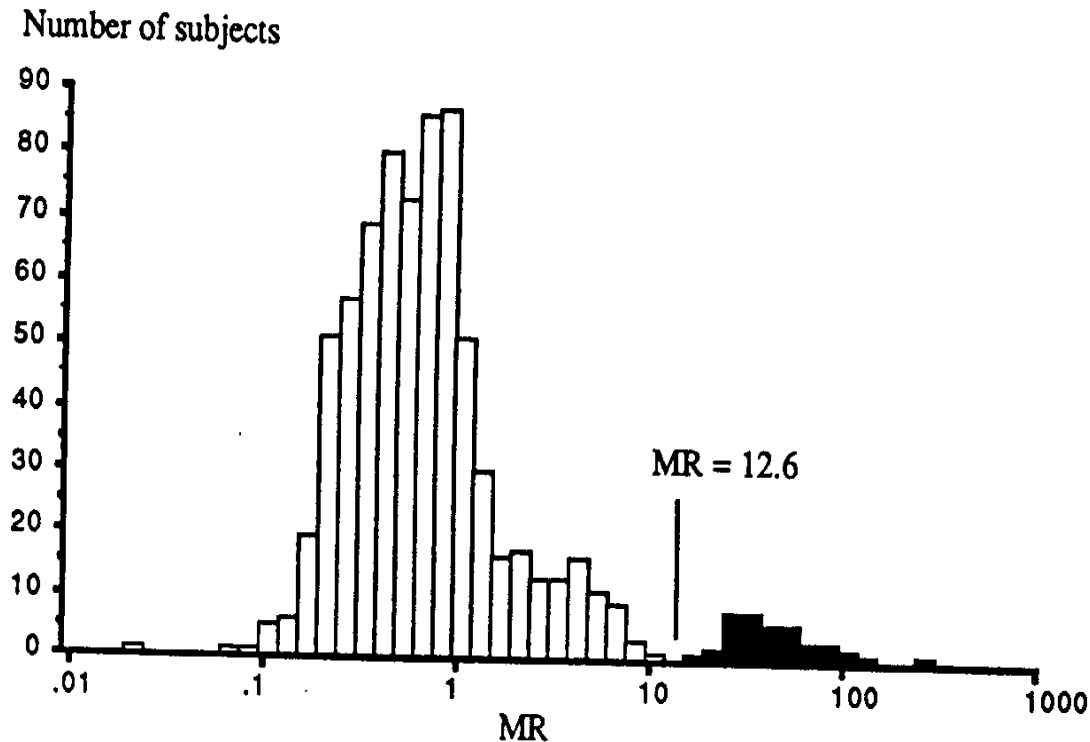
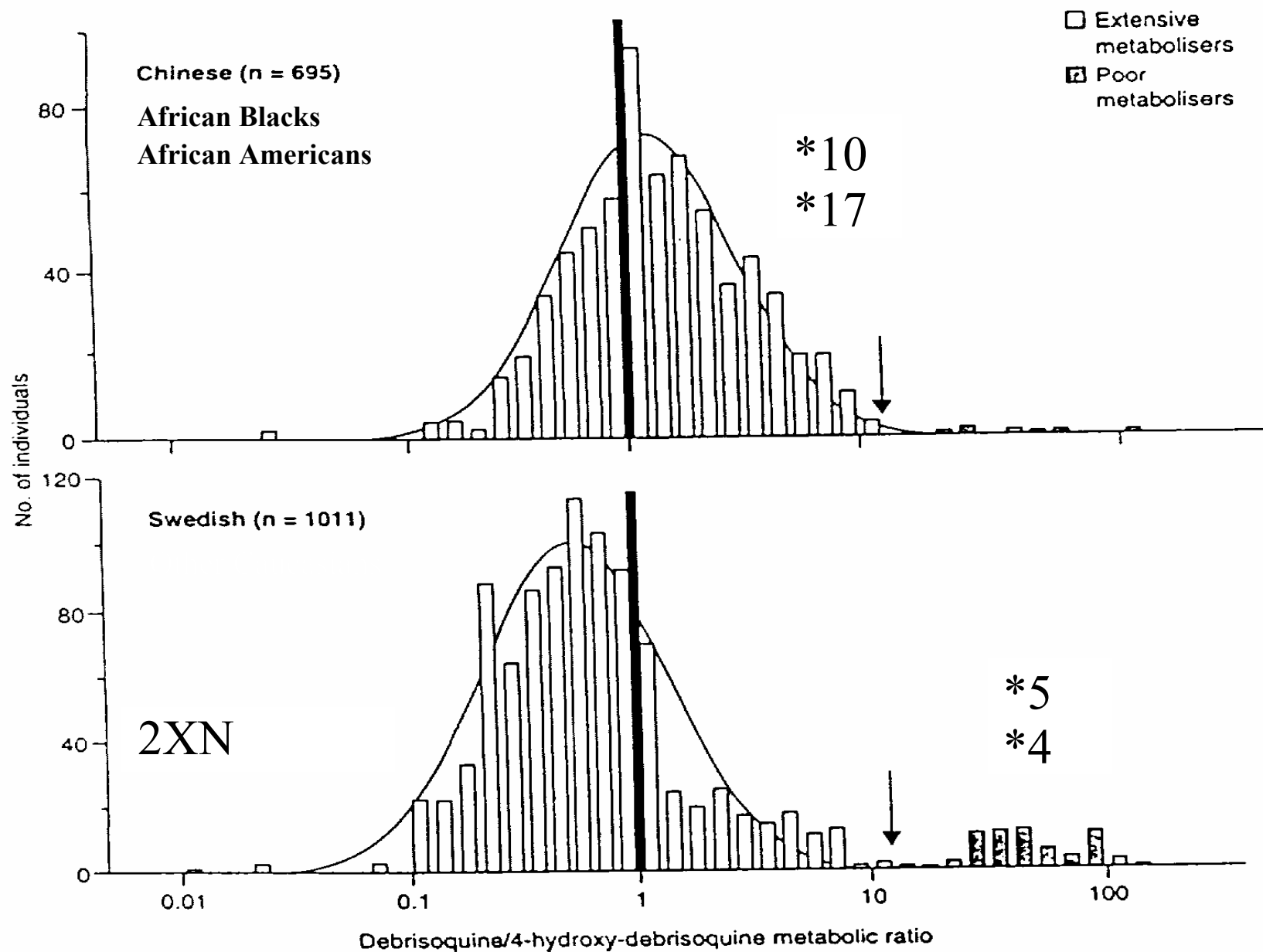
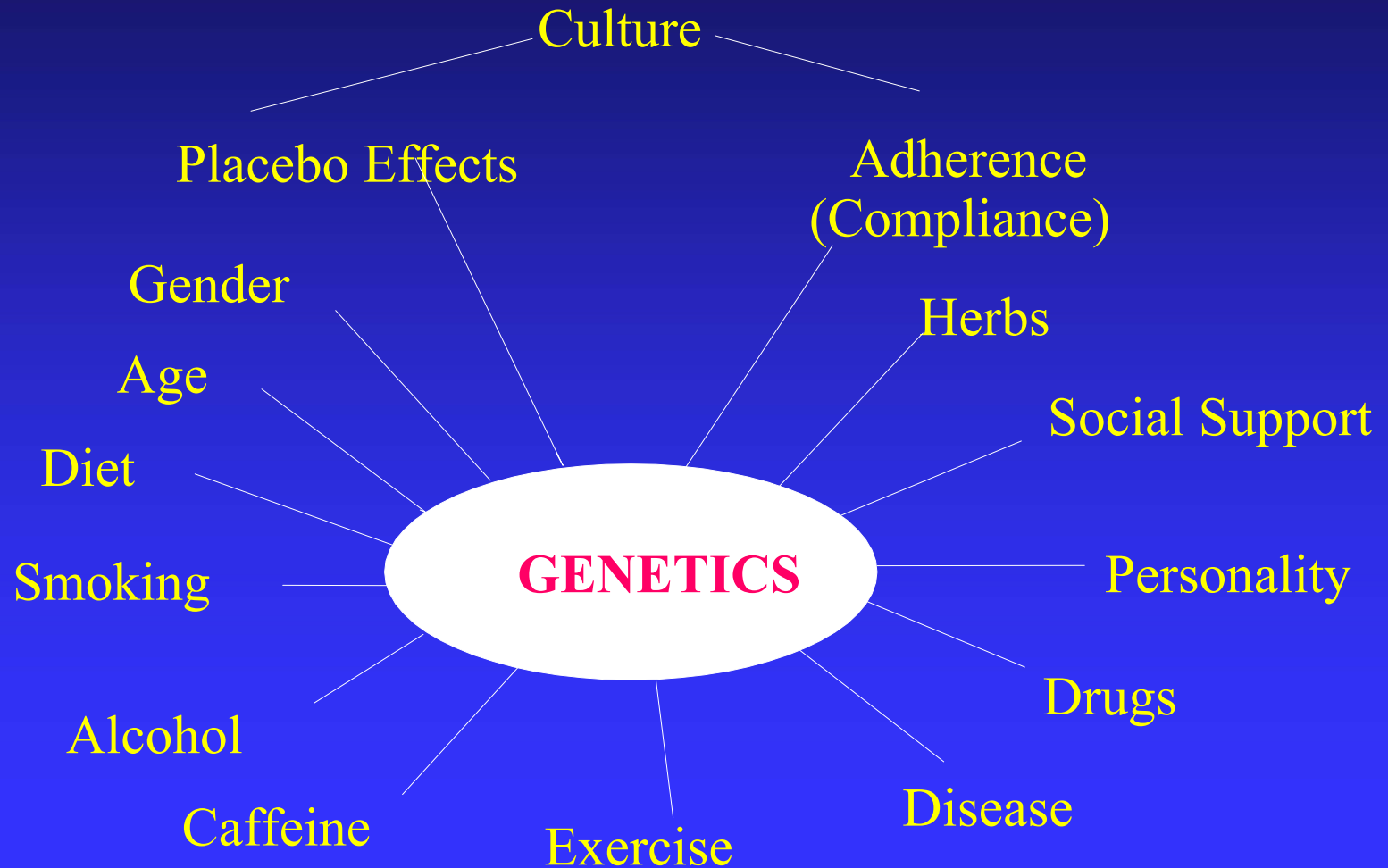


Fig. 1. Distribution of the urinary D/4-OH-D MRs among 757 white Swedish subjects. *Open bars* indicate rapid hydroxylators; *solid bars* indicate slow hydroxylators.

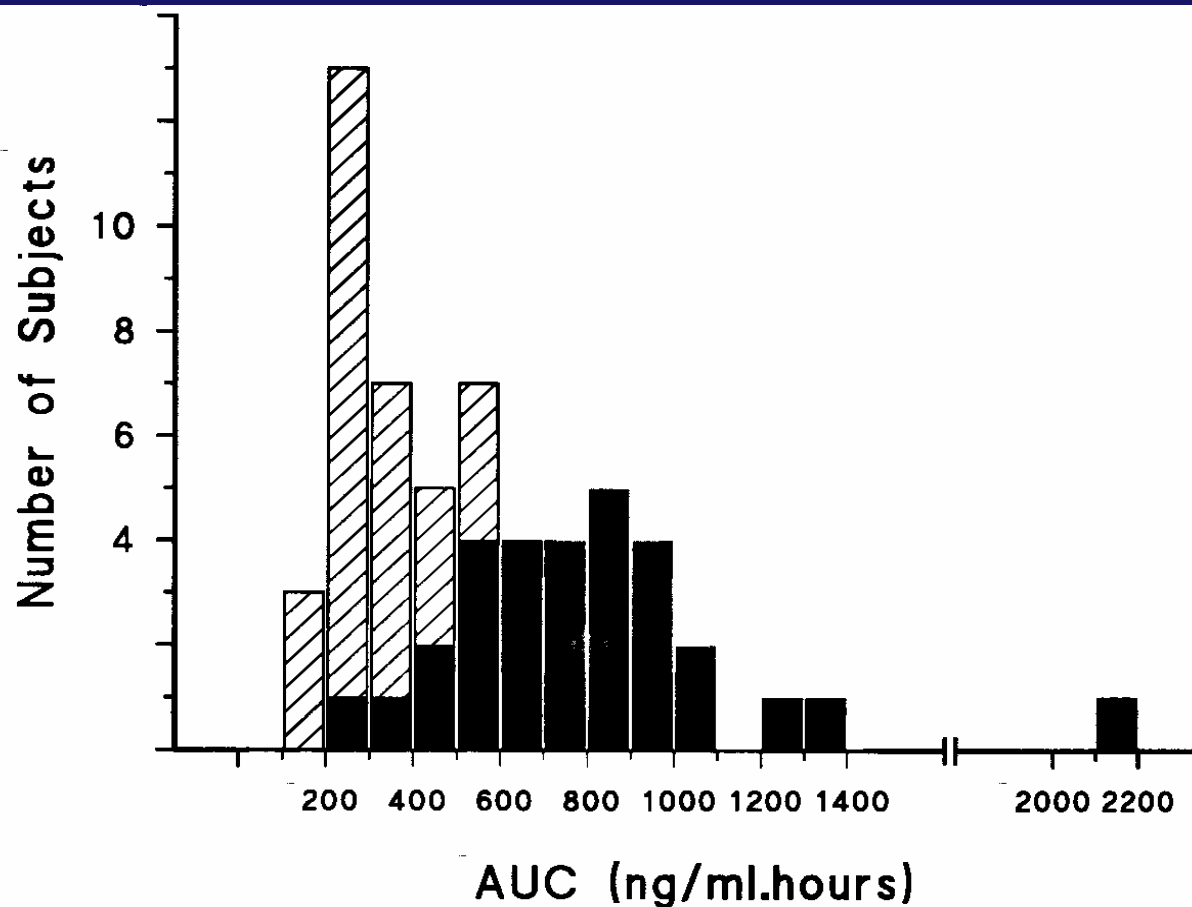


**Fig. 2.** Distribution of the urinary debrisoquine/4-hydroxy-debrisoquine metabolic ratio (MR) in 695 Chinese and 1011 Swedish Caucasian healthy individuals. The arrows indicate a MR of 12.6, the antimode between extensive metabolisers and poor metabolisers as established in Caucasian populations. A line is drawn at a MR of 1.0. Most Chinese extensive metabolisers have a MR > 1, while most Swedish extensive metabolisers have a MR < 1 (reproduced from Berilsson et al.,<sup>[14]</sup> with permission).

# FACTORS AFFECTING DRUG RESPONSE

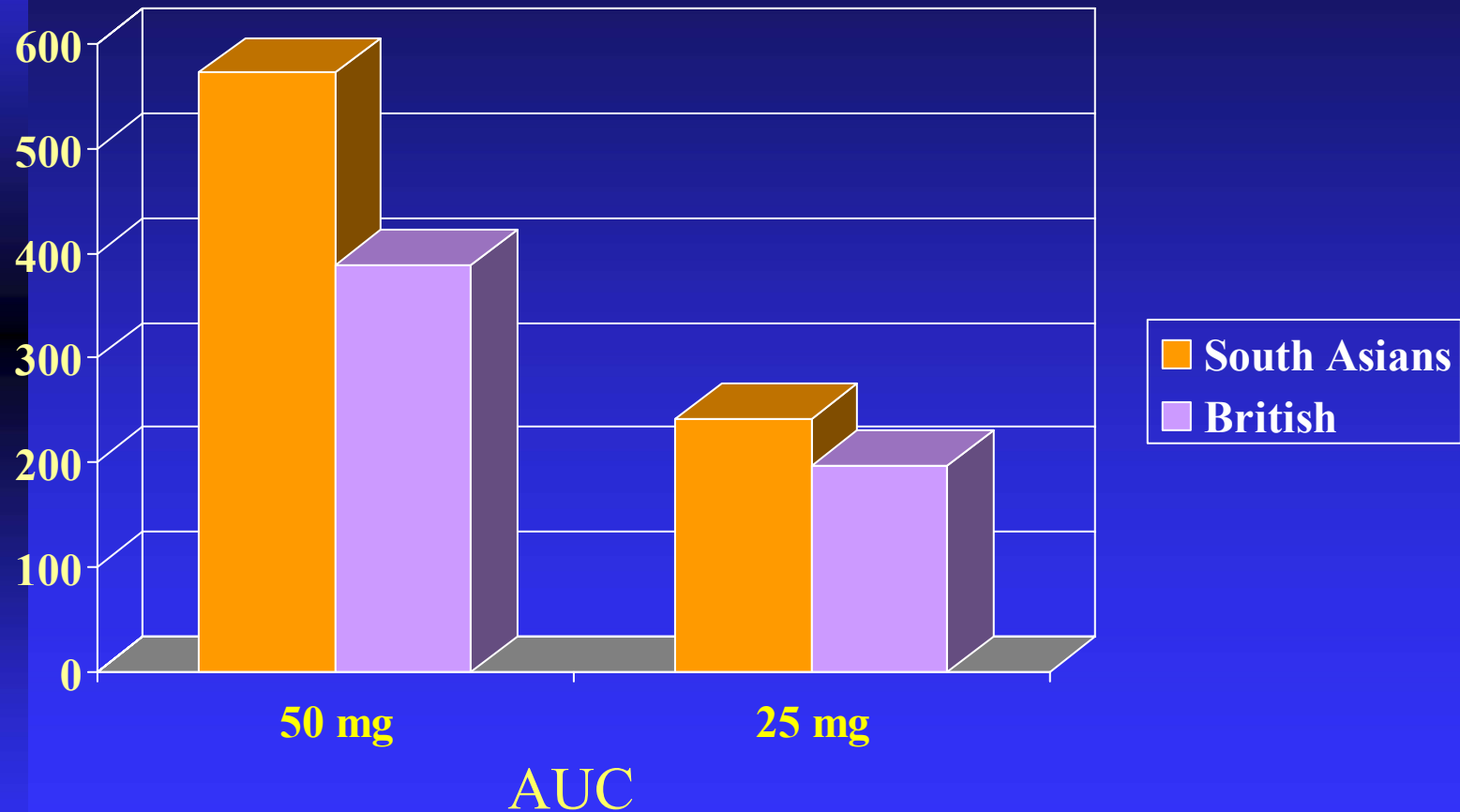


# NIFEDIPINE METABOLISM IN ASIAN INDIANS AND BRITISH WHITES



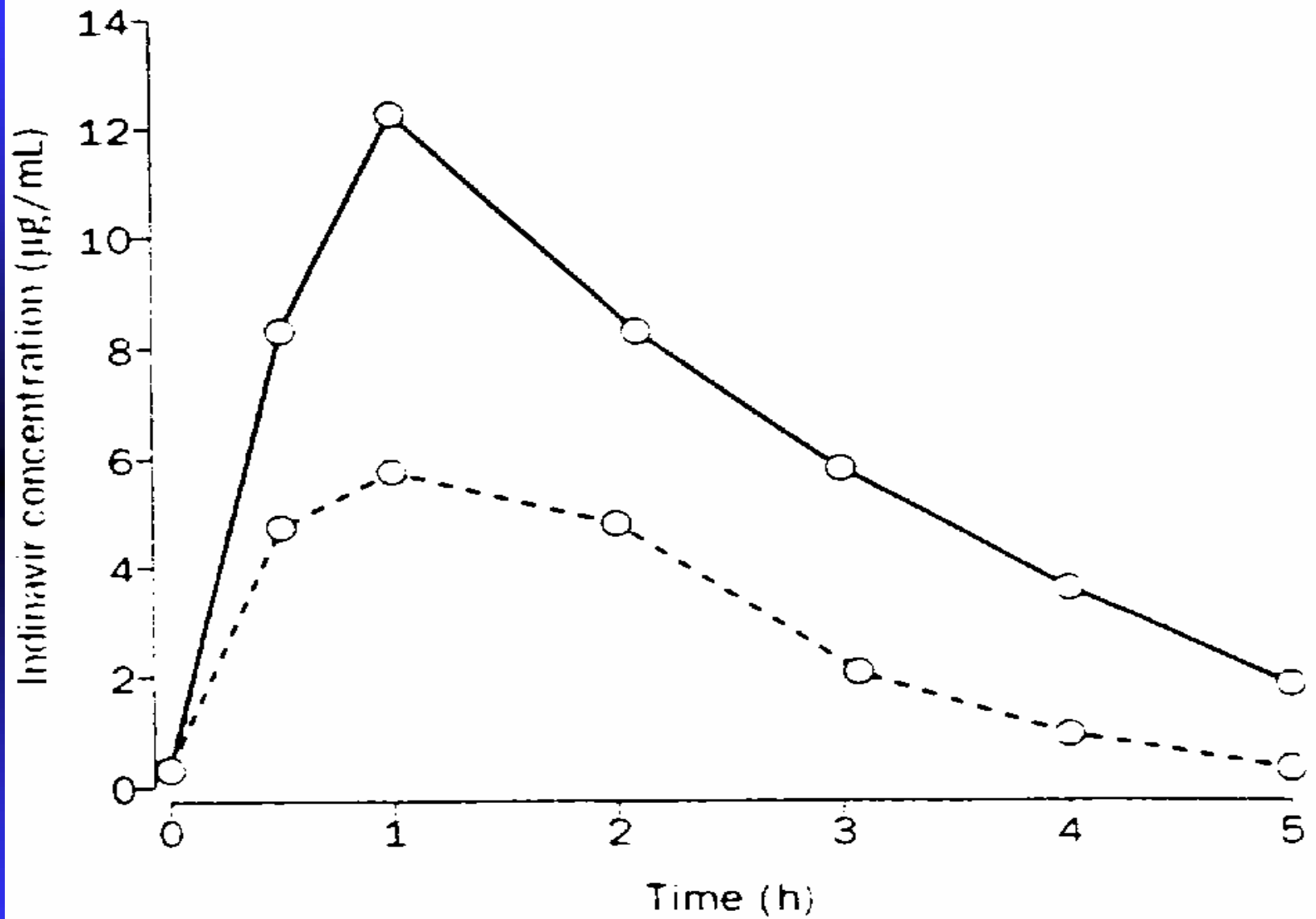
**Fig. 2.** Distribution of values for area under the plasma concentration–time curve (AUC) for nifedipine in Caucasian subjects (*hatched bars*) and in South Asian subjects (*solid bars*).

# Clomipramine Concentration: South Asians vs British Whites



Lewis P, Rack PH, Vaddadi KS, Allen JJ (1980) Postgraduate Medical Journal 56 (Suppl. 1): 46-49

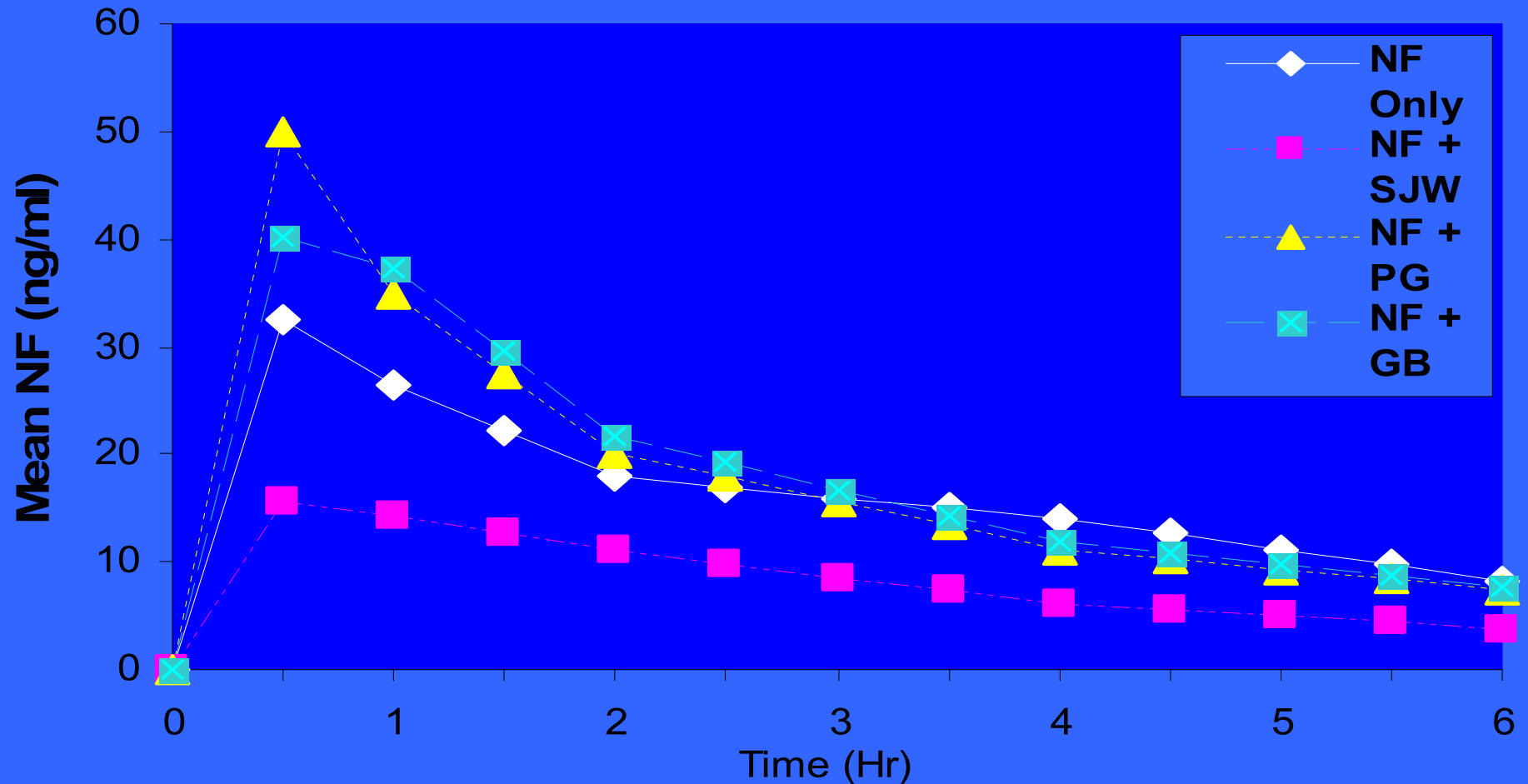




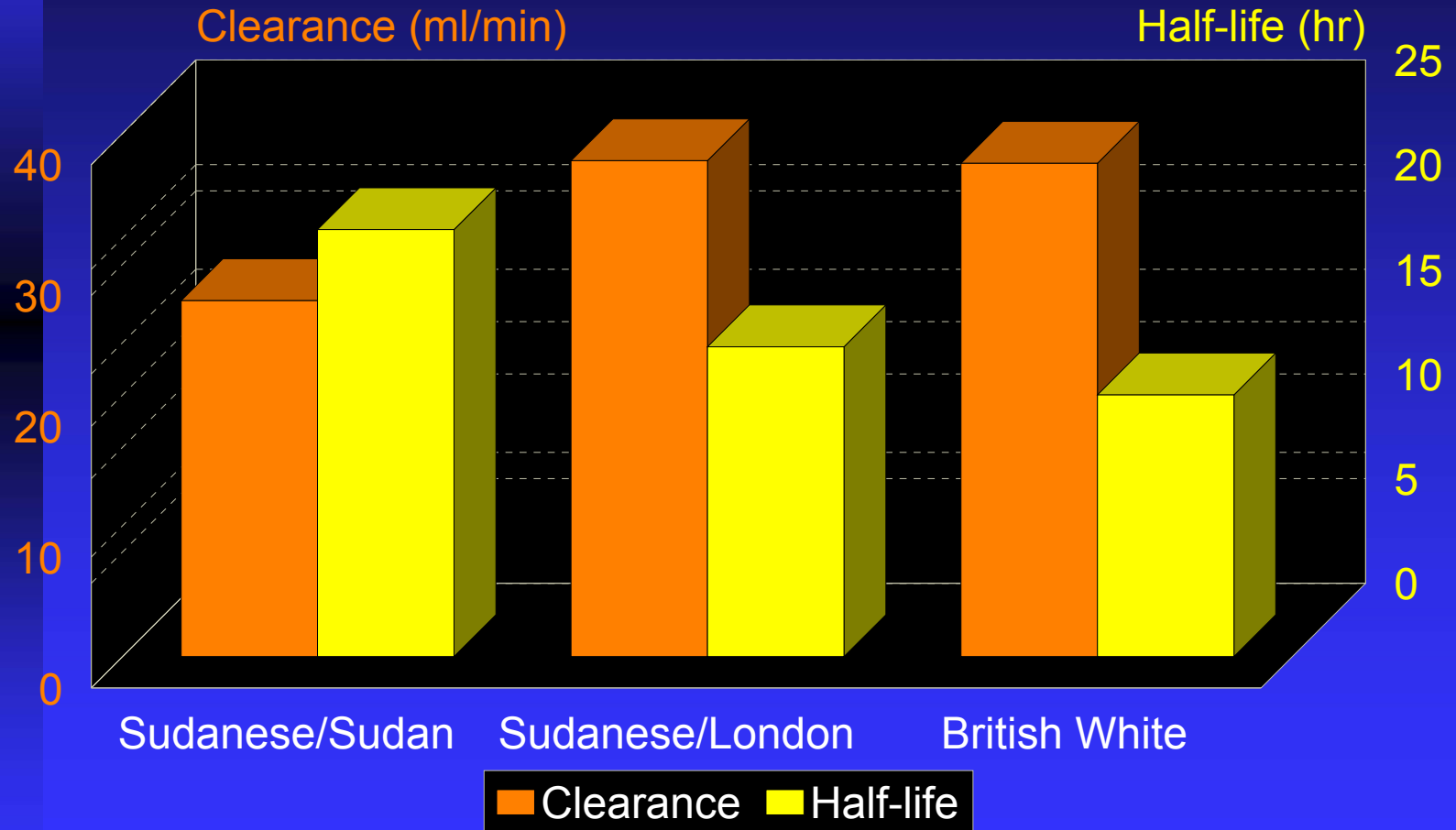
**Mean concentration-time of Indinavir alone (solid line) and with concomitant St John's wort (dotted line)**



# Nifedipine-Herb Interactions: Nifedipine Plasma Levels (ng/ml)



## PHARMACOKINETICS OF ANTIPYRINE: SUDANESE AND BRITISH



Paroxetine  
Citalopram, etc

Reboxetine  
Desipramine, etc

Serotonin  
Transporter

Norepinephrine  
Transporter

Serotonin  
system

Norepinephrine  
system

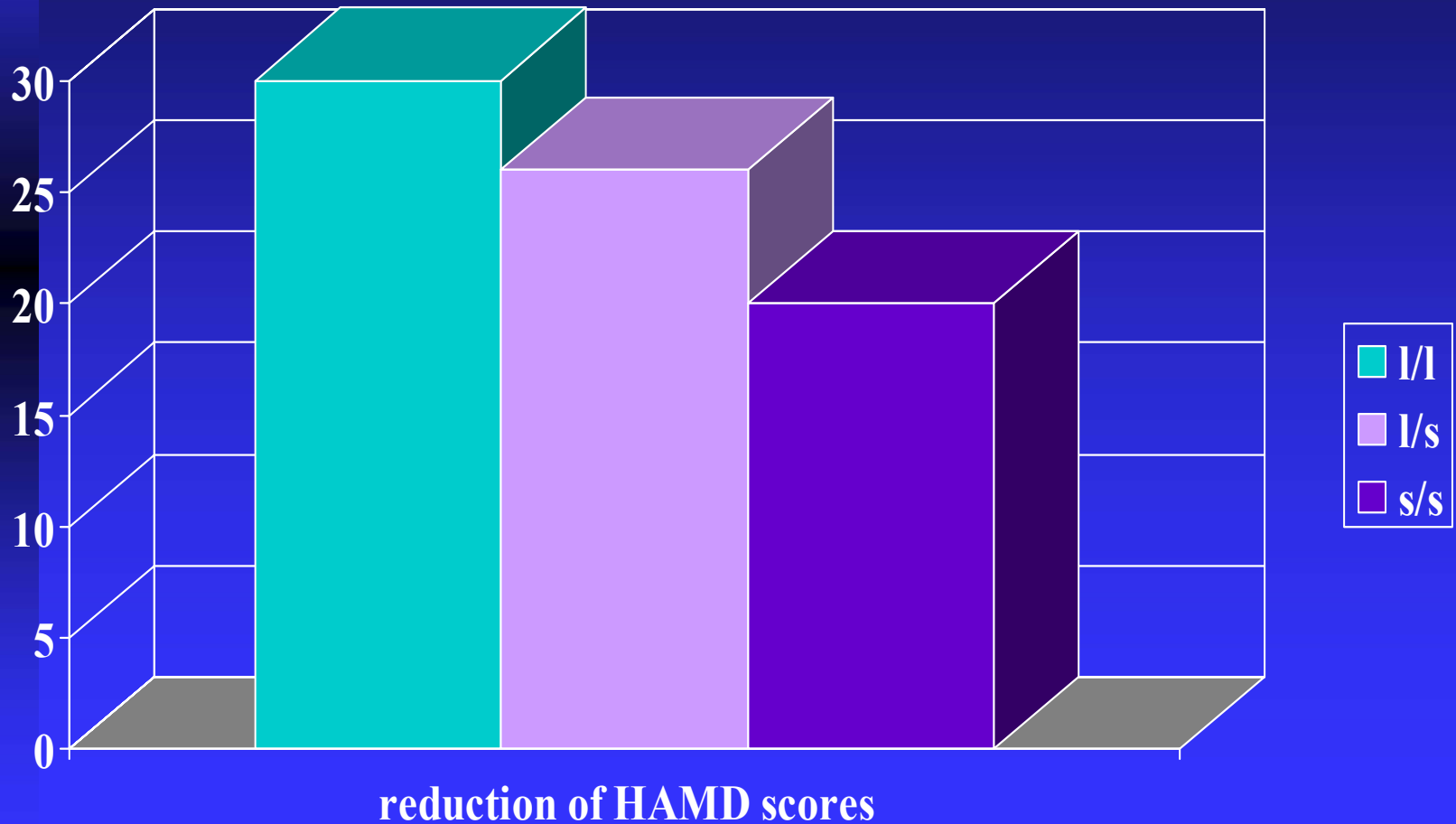


# Relationship between Serotonin Transporter (SERT or 5-HTT; SLC6A4) Polymorphism and Antidepressant Response

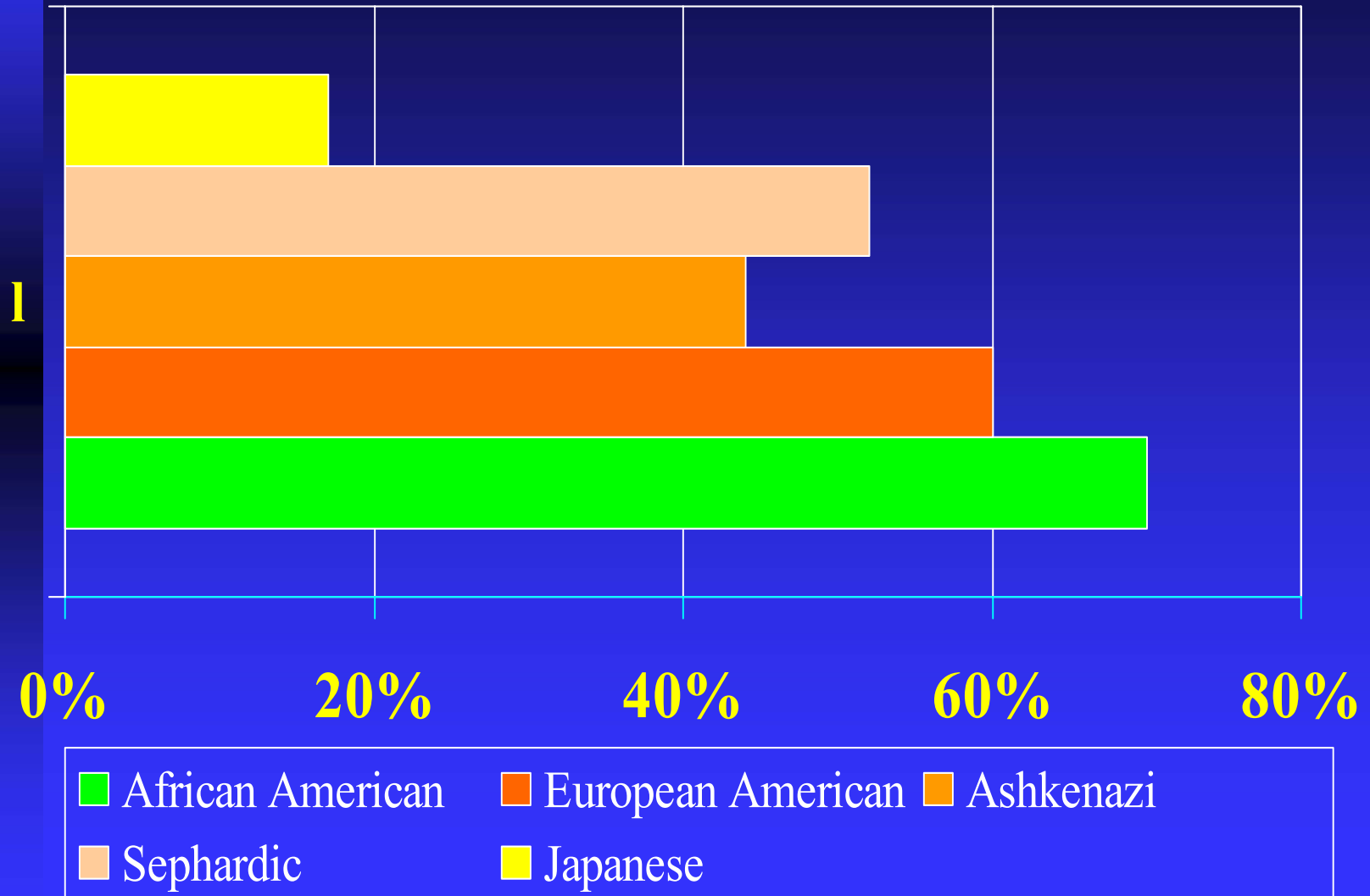
## Diallelic promoter polymorphism (*l* and *s* alleles)

- Subjects with long variant (*l*) showed twice the basal transcriptional activity
- In Caucasians, long variant (*l*) is associated with better and faster response to SSRI's, such as paroxetine and fluvoxamine

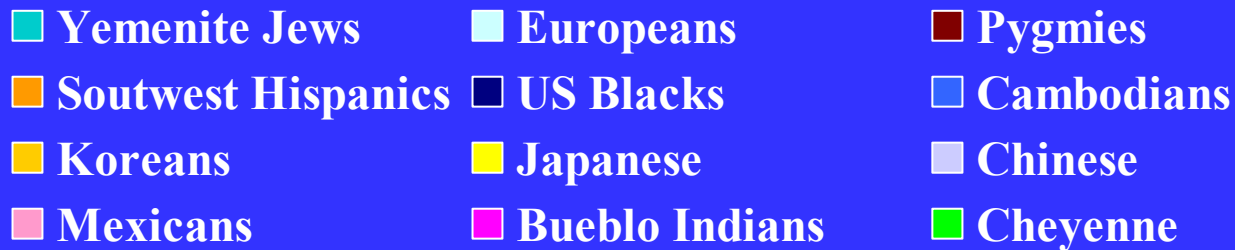
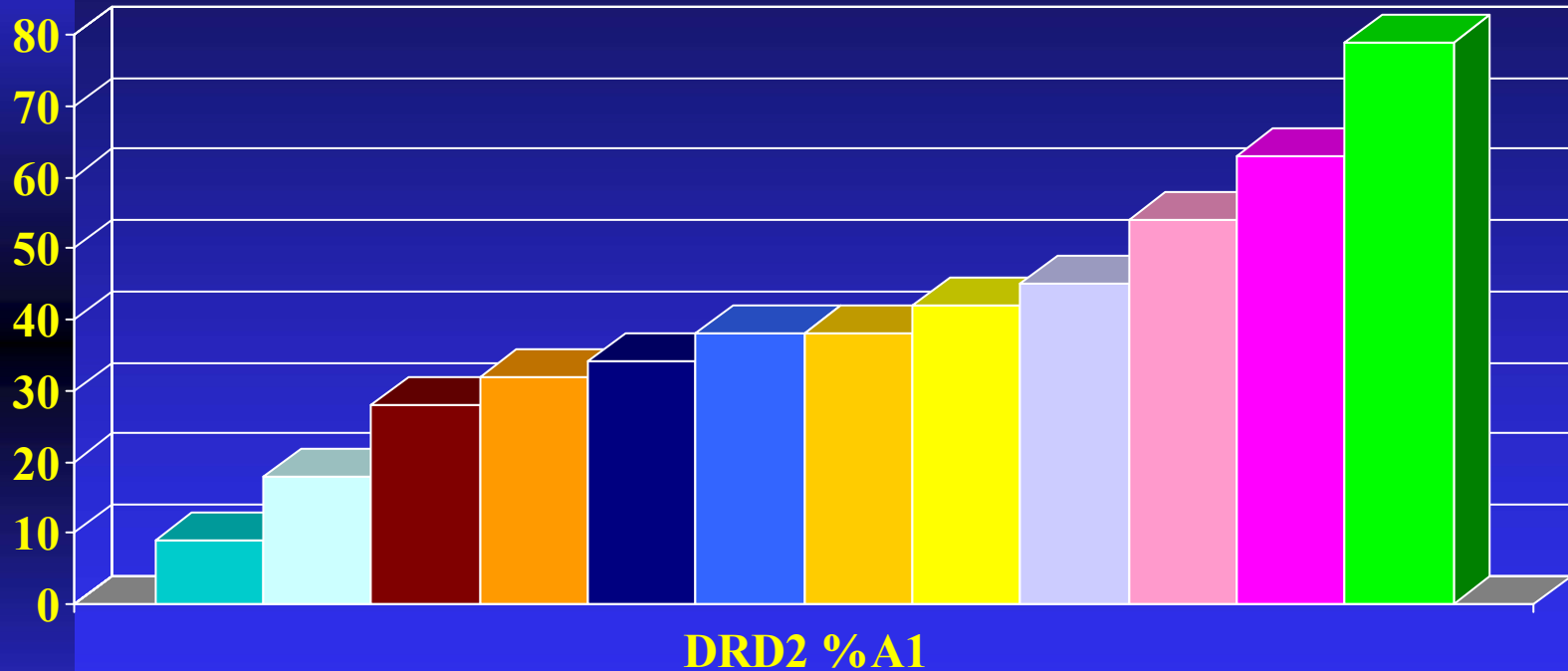
# 5HTT POLYMORPHISM AND RESPONSE TO FLUVOXAMINE



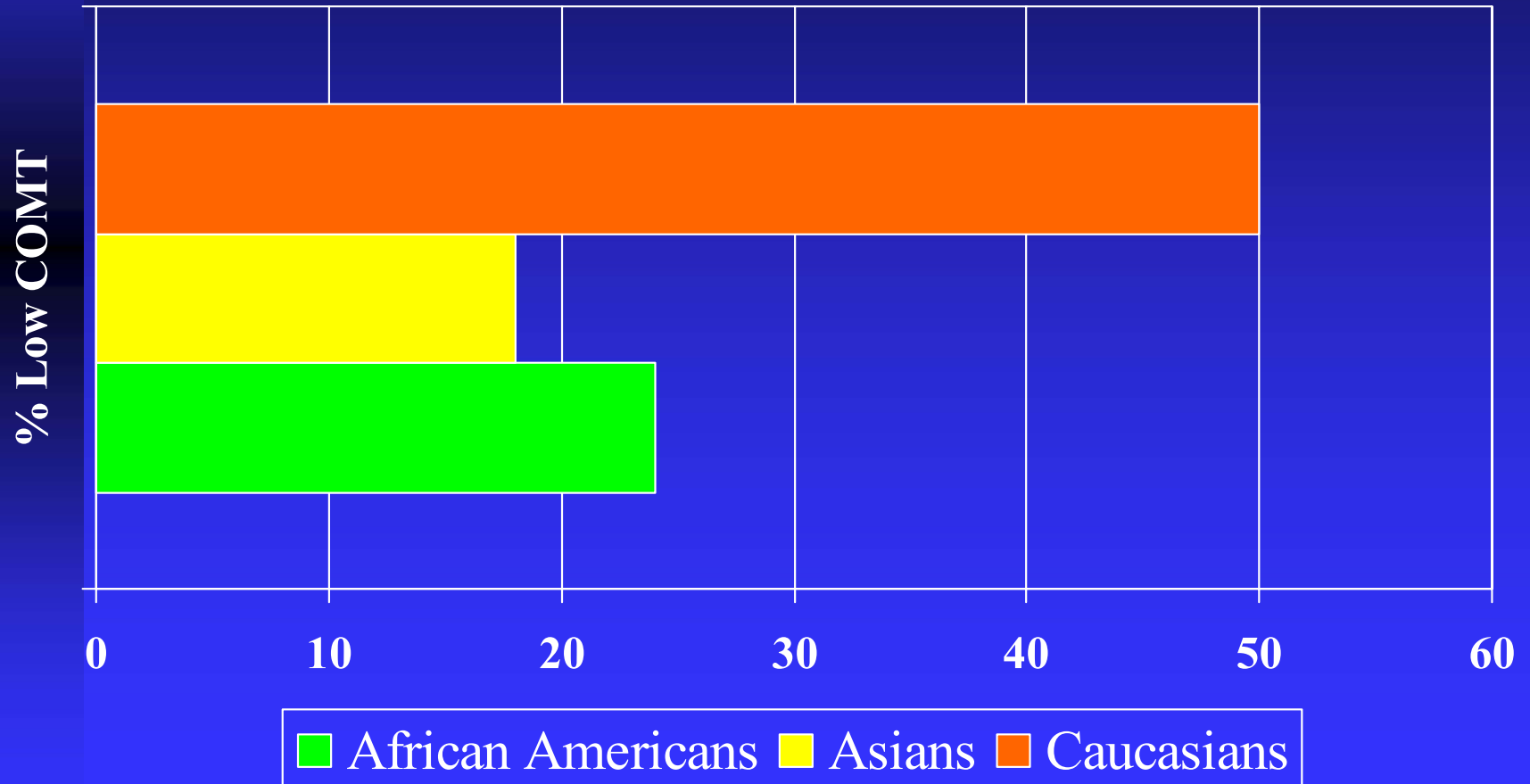
# Serotonin Transporter Gene (SLC6A4) Polymorphism



# Dopamine D2 Receptor Gene Polymorphism



# CATECHOL-*O*-METHYLTRANSFERASE (COMT) POLYMORPHISM

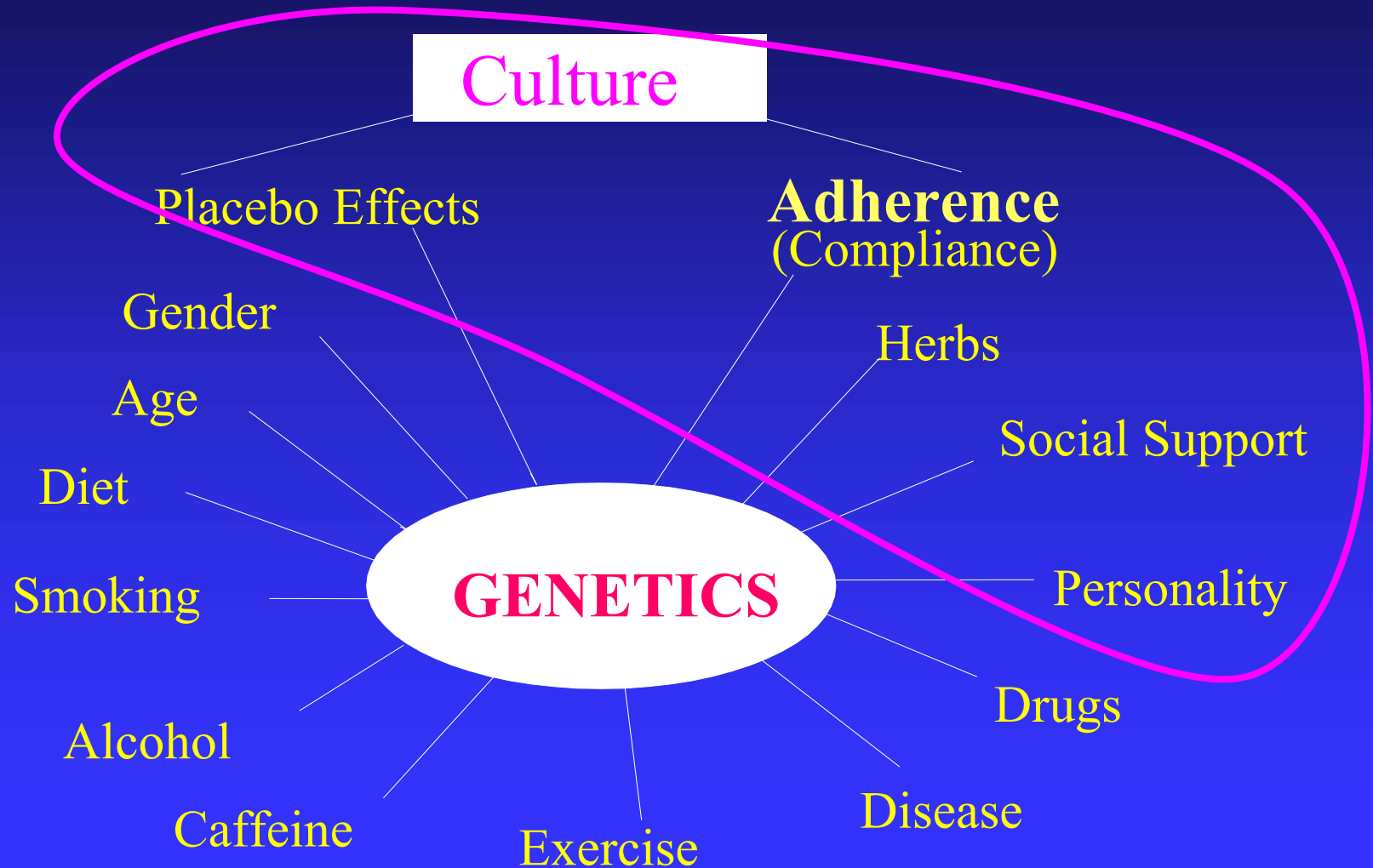




# Genetic Variations within and across Populations

- Variations extremely prevalent
- Responsible for inter-individual and cross-ethnic variations in biological and behavioral traits
- Responsible for the risks of all complex health problems, including all psychiatric conditions, as well as most of the chronic medical problems, such as diabetes and hypertension
- These associations may be ethnically specific. Thus, findings from one ethnic group can not be applied to other groups until proven
- Determines pharmacological treatment response

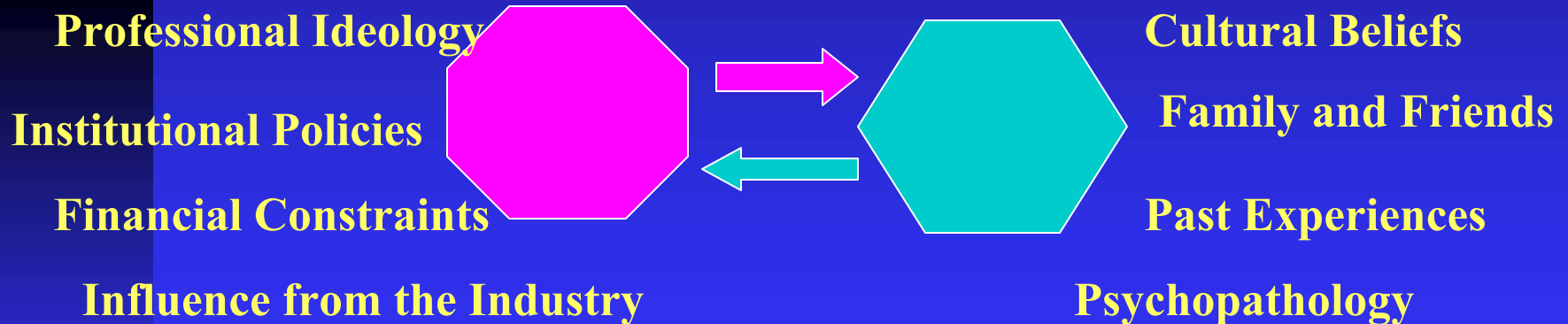
# FACTORS AFFECTING DRUG RESPONSE



# *PSYCHOPHARMACOLOGY IN THE SOCIOCULTURAL CONTEXT*

**Clinician**

**Patient**



# Future Directions

## ■ Technological advances

- ◆ Gene array methodologies
- ◆ Cell biology
- ◆ Neuroscience

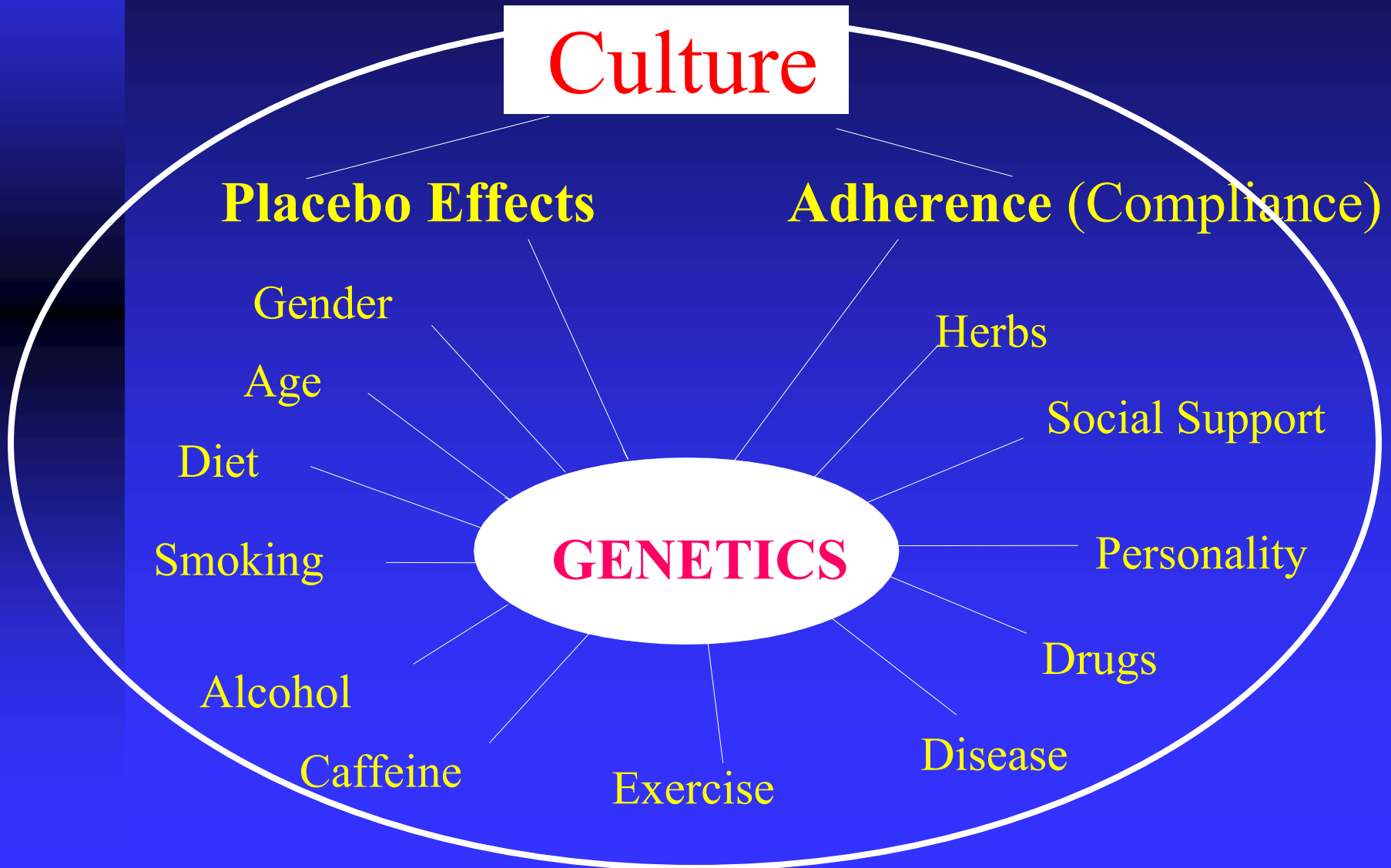
## ■ Clinical advances

- ◆ Alternative ways for conceptualizing clinical phenomena
- ◆ Assessment of individual differences

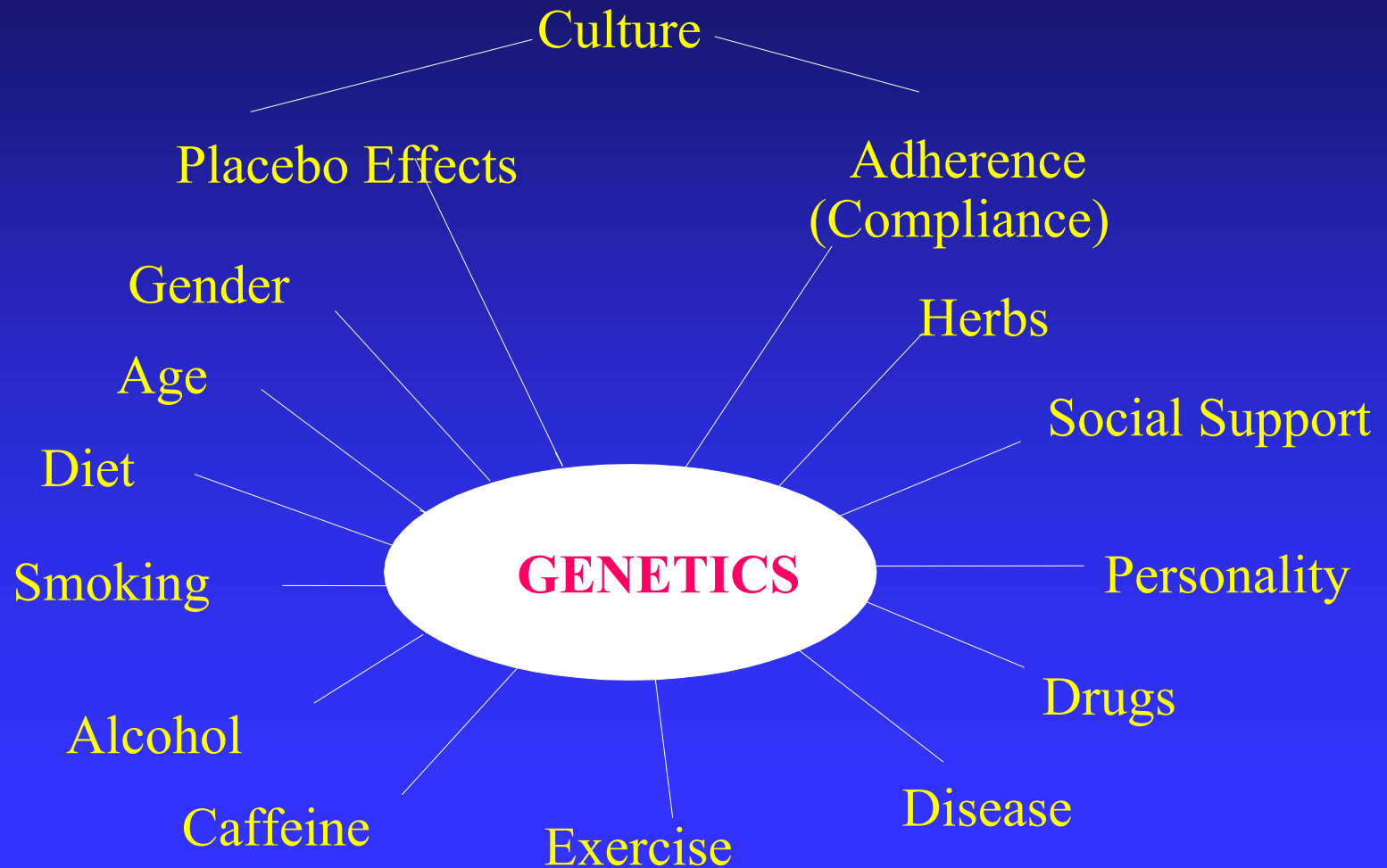
## ■ Research on the Socio-cultural Context of Psychopharmacological Practice



# FACTORS AFFECTING DRUG RESPONSE



# FACTORS AFFECTING DRUG RESPONSE

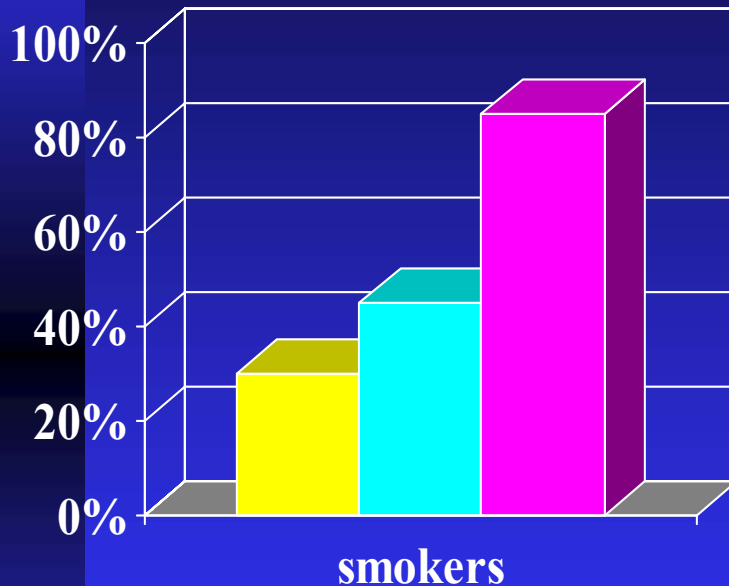


# Ethnic Variations in Antidepressant Response

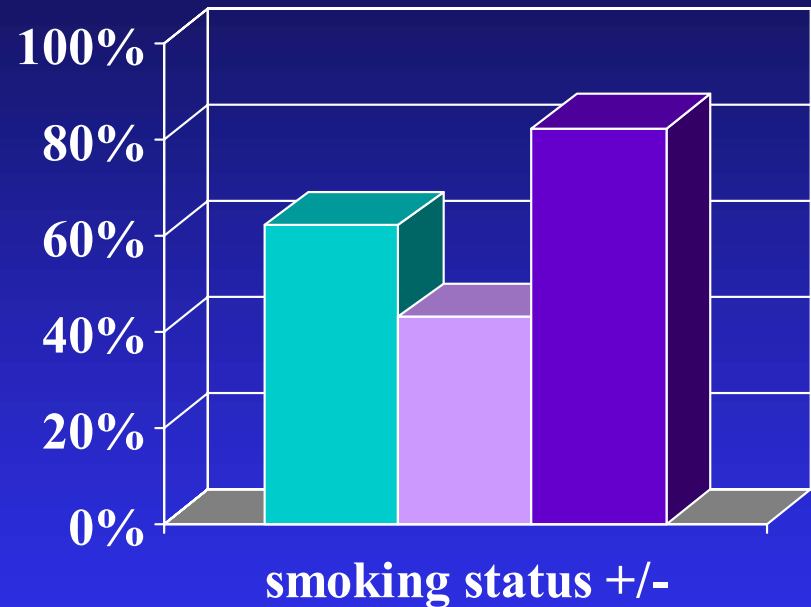
- A three site collaborative RO1 project (2001-2006)
- Subjects recruited from three sites with identical criteria and treated with identical protocol
  - ◆ Harbor-UC LA Medical Center
  - ◆ King-Drew Medical Center
  - ◆ Cedars-Sinai Medical Center
- 400 subjects with DSM-IV major depression: 200 African Americans vs 200 Caucasians
- Patients treated with citalopram for 8 weeks
- Pharmacogenetic profiles as predictors of response
  - ◆ Serotonin transporter polymorphism
  - ◆ CYP2C19 and CYP3A4



# SMOKING AND ANTIPSYCHOTIC RESPONSES



■ normal  
■ depressed  
■ schizophrenic



■ haloperidol  
■ fluphenazine decanoate  
■ clozapine

# Monoamine Hypothesis for Mood Disorders

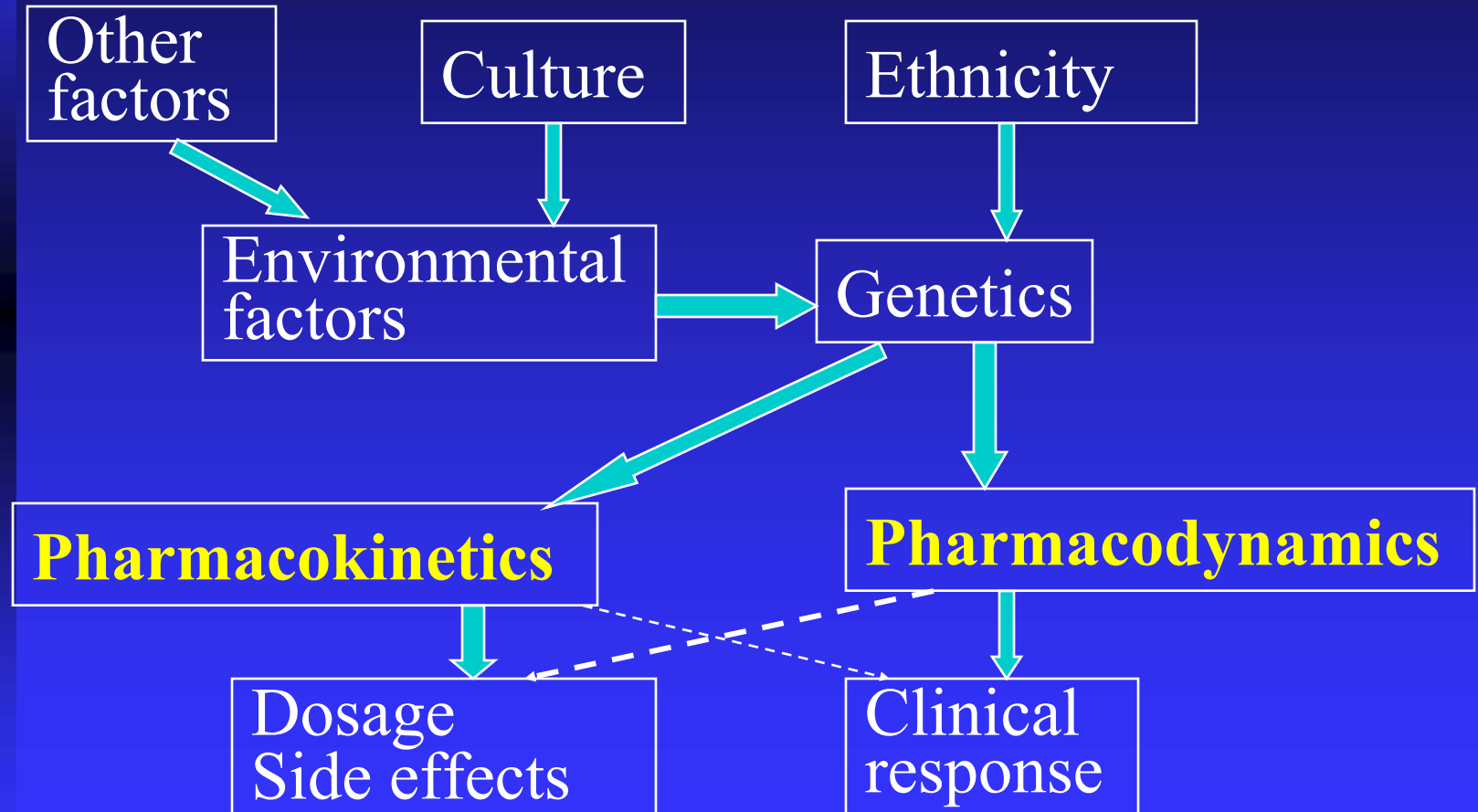
## ■ Neurotransmitters

- ◆ Serotonin, Norepinephrine, Dopamine, etc

## ■ Systems Involved in the Regulation of the Effects of Neurotransmitters

- ◆ Transporters (e.g. **Serotonin Transporter**)
- ◆ Receptors
- ◆ Monoamine synthesis and removal (e.g., **CATECHOL-O-METHYLTRANSFERASE [COMT]**)

# Factors Determining Pharmacological Response



# CYTOCHROME P450 ENZYMES

- Most psychotropics metabolized by one or more of the following four:
  - CYP2D6
  - CYP3A4
  - CYP1A2
  - CYP2C19
- Dramatic individual and ethnic variations in all, caused by differences in the frequency of functional alleles
- Inhibition common with all
- Induction common with CYP3A4 and CYP1A2

# Variations in pharmacogenetic profiles across populations of “African” origin

# Ethnic Variations in Antidepressant Response

- A trial of citalopram in African-American and European-American Patients with DSM-IV Major Depression
- Clinical outcome assessed 8-week trial
  - ◆ Measures of depression: HAM-D and BDI
  - ◆ Side effect profiles: TESS and ASEX
  - ◆ Others: CGI, PGI
- Harvest leukocytes
  - ◆ Creating immortalized cell lines
  - ◆ Extraction of DNA
- Determination of genotypes
  - ◆ SERT
  - ◆ CYP2C19
- Serum drug levels

# Genetic Variations within and across Populations

- Variations extremely prevalent
- Responsible for inter-individual and cross-ethnic variations in biological and behavioral traits
- Responsible for the risks of all complex health problems, including all psychiatric conditions, as well as most of the chronic medical problems, such as diabetes and hypertension
- Determines pharmacological treatment response

# The Role of Ethnicity in Determining Pharmacological Responses

## ■ Three classical examples

- ◆ “Primaquine hemolysis”
- ◆ Isonizid toxicity
- ◆ “Flushing response” to alcohol

## ■ More recent studies



# Hemolytic Anemia and Glucose-6-Phosphatase Dehydrogenase Deficiency

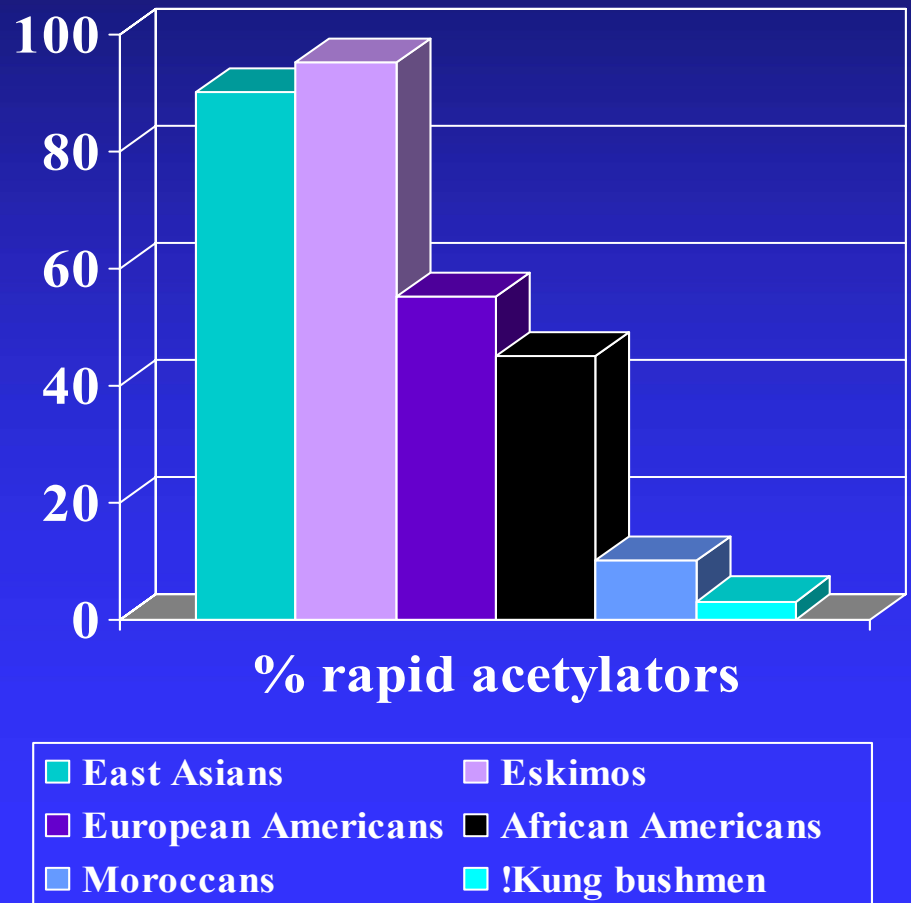
- “Primaquine hemolysis”
- Other oxidant drugs
- Fava beans
- Caused by hemoglobin variants
- Prevalent in people of African, Mediterranean and Southeast Asian origins

# Isoniazid Toxicity

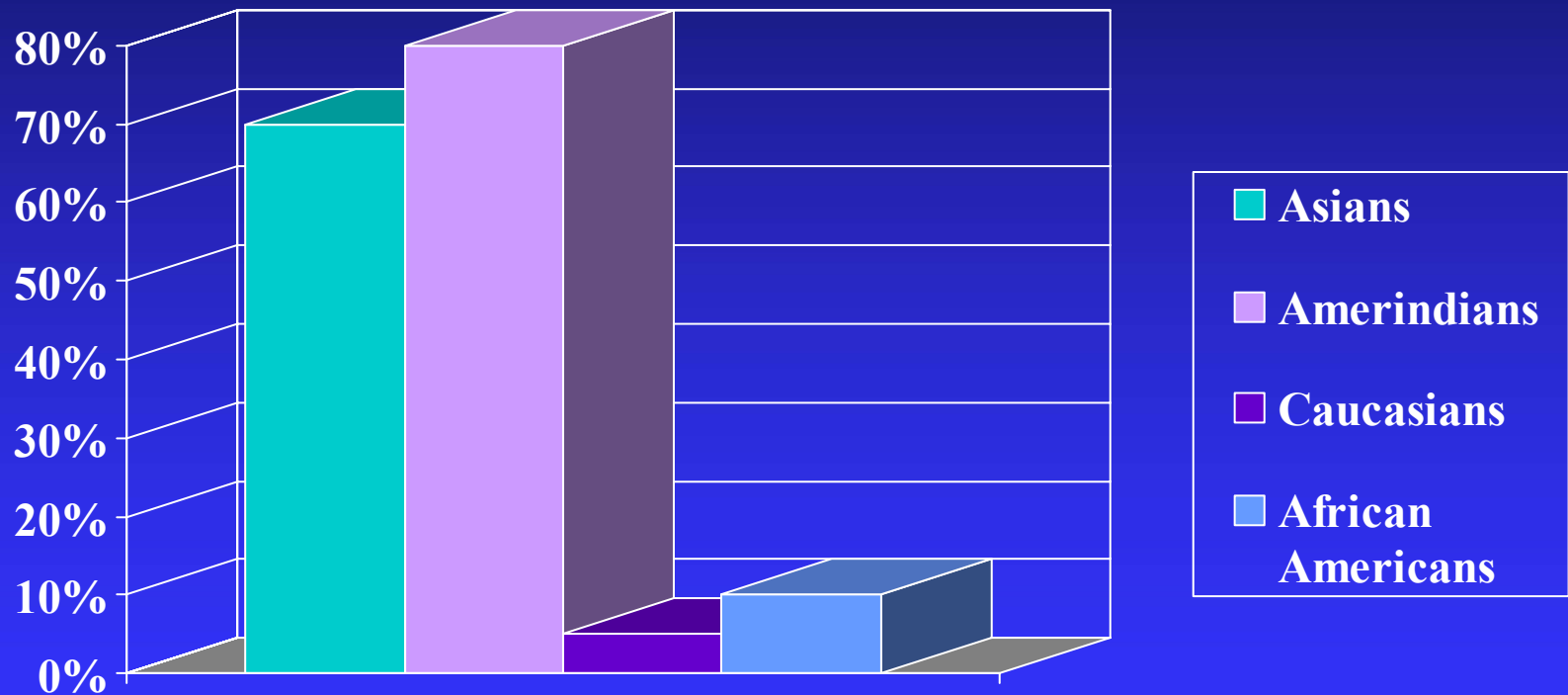
- Acetylation status is associated with different types of side effects
  - ◆ Hepatotoxicity - rapid acetylators
  - ◆ Peripheral neuritis - slow acetylators
- The distribution of the acetylation status varies significantly across ethnic groups:

# Isoniazid Toxicity

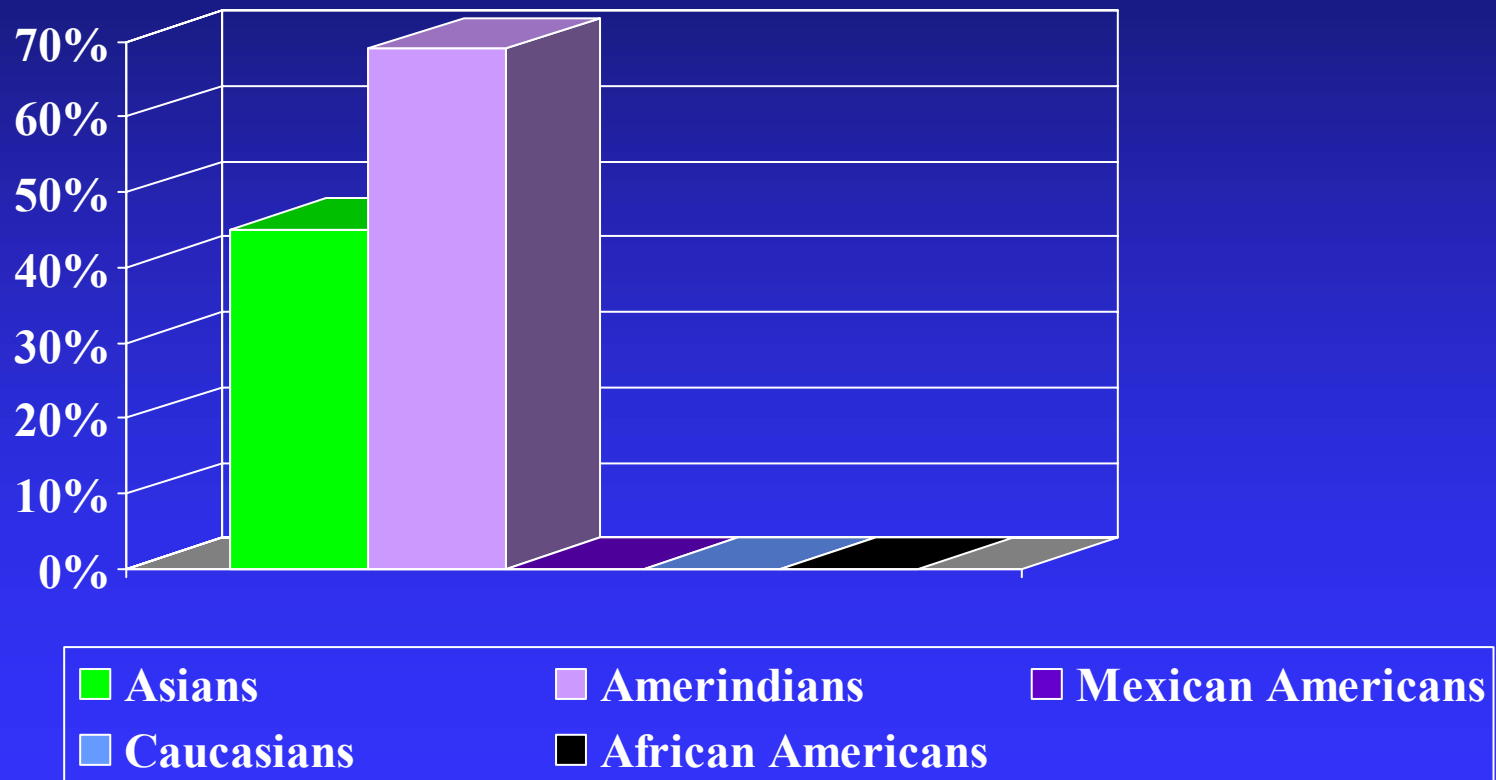
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  - ◆ rapid acetylators: Hepatotoxicity
  - ◆ Peripheral neuritis: slow acetylators



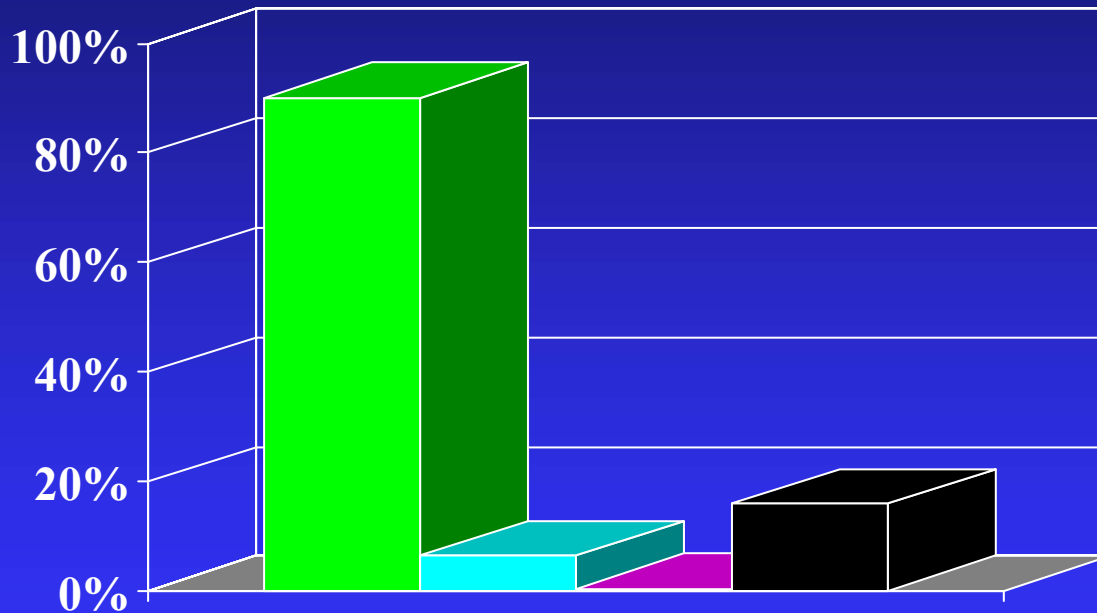
# PREVALENCE OF FLUSHING RESPONSE BY ETHNCIITY



# PREVALENCE OF ACETALDEHYDE DEHYDROGENASE (ALDH) BY ETHNICITY

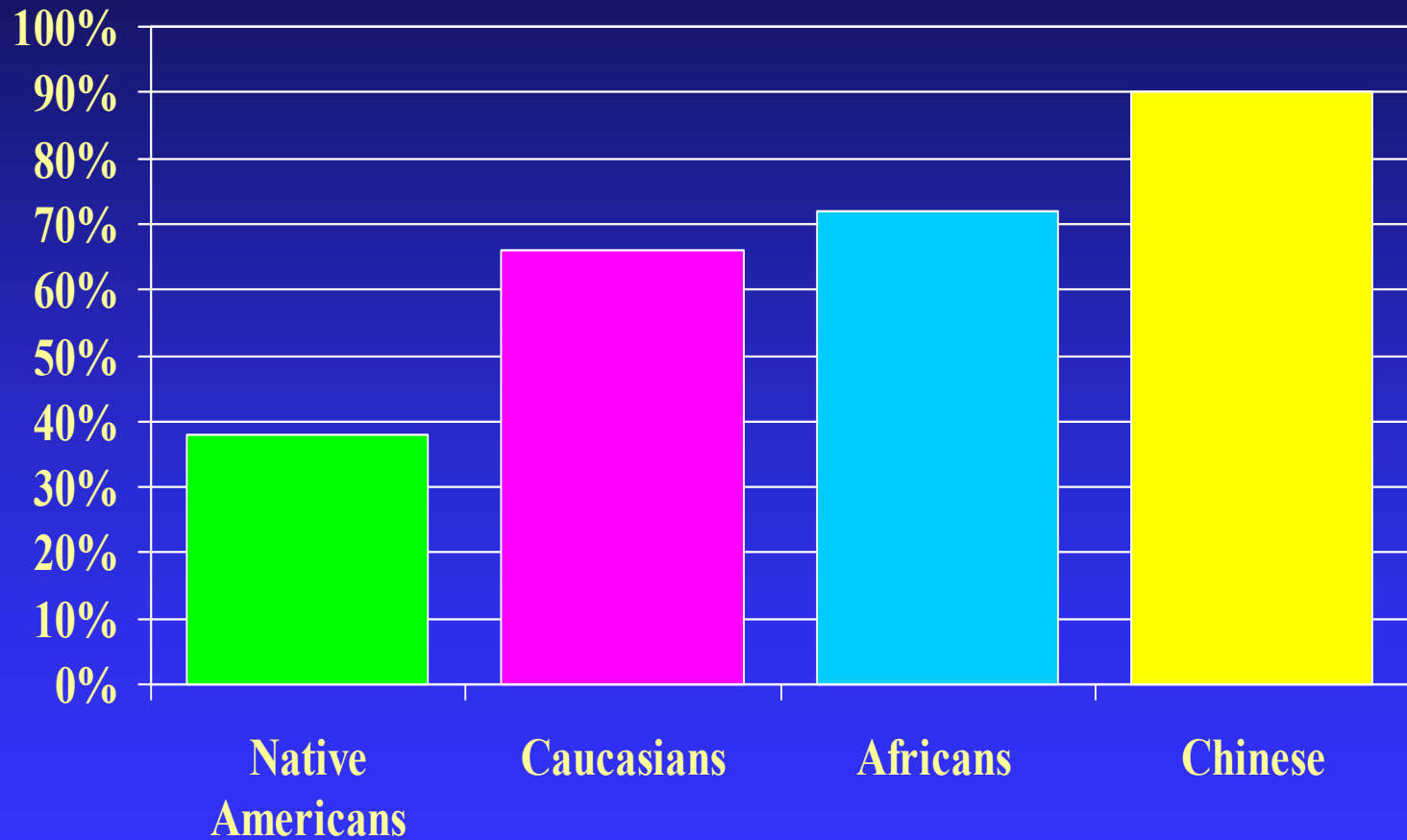


# PREVALENCE OF ALCOHOL DEHYDROGENASE (ADH) BY ETHNICITY

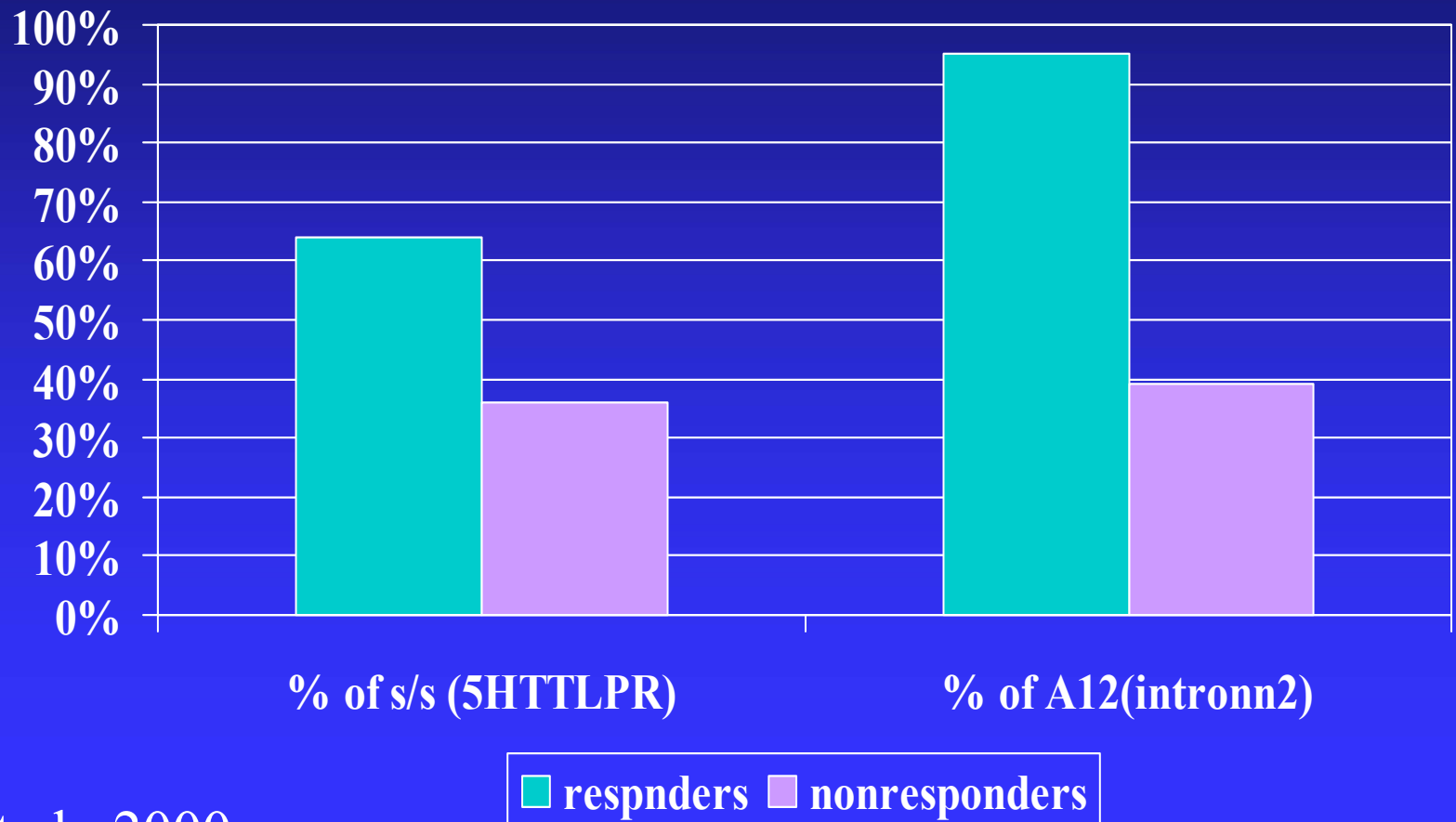


■ Asians ■ Mexican Americans ■ Caucasians ■ African Americans

# Frequency of the A12 Allele in Intron 2 of the Serotonin Transporter (SERT) in Normal Volunteers



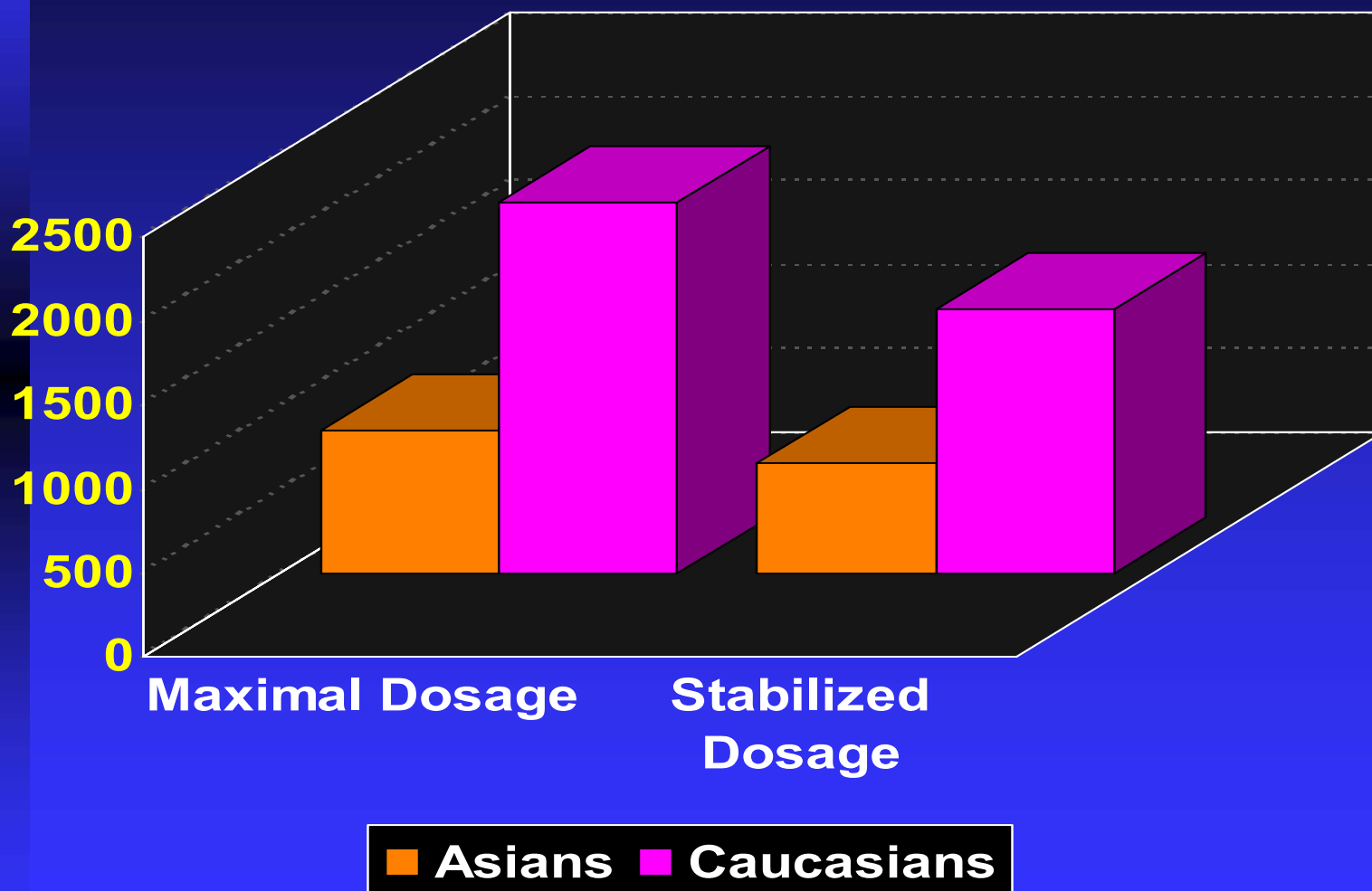
# Serotonin Transporter (SERT) and Antidepressant Response in Asians



Kim et al., 2000

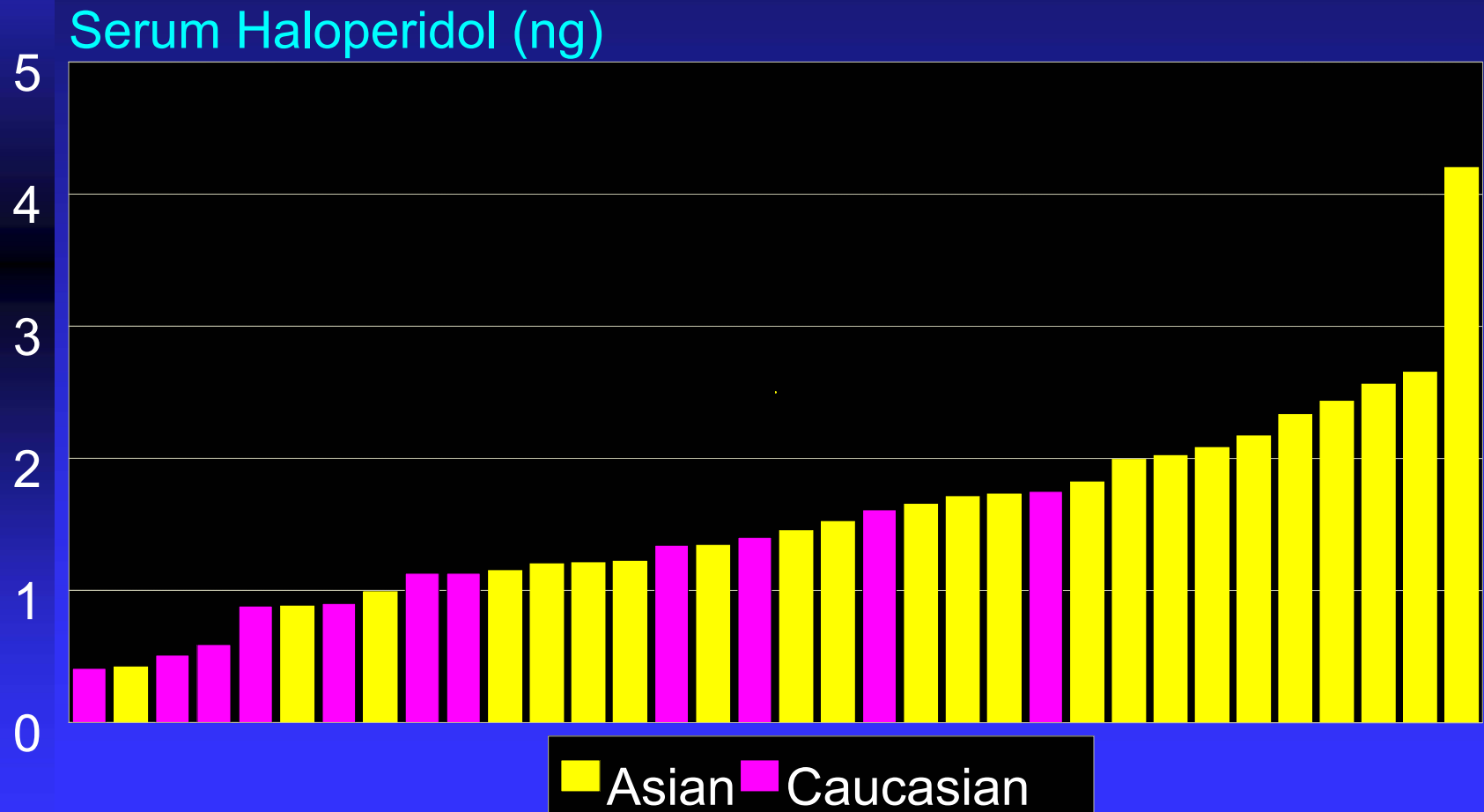


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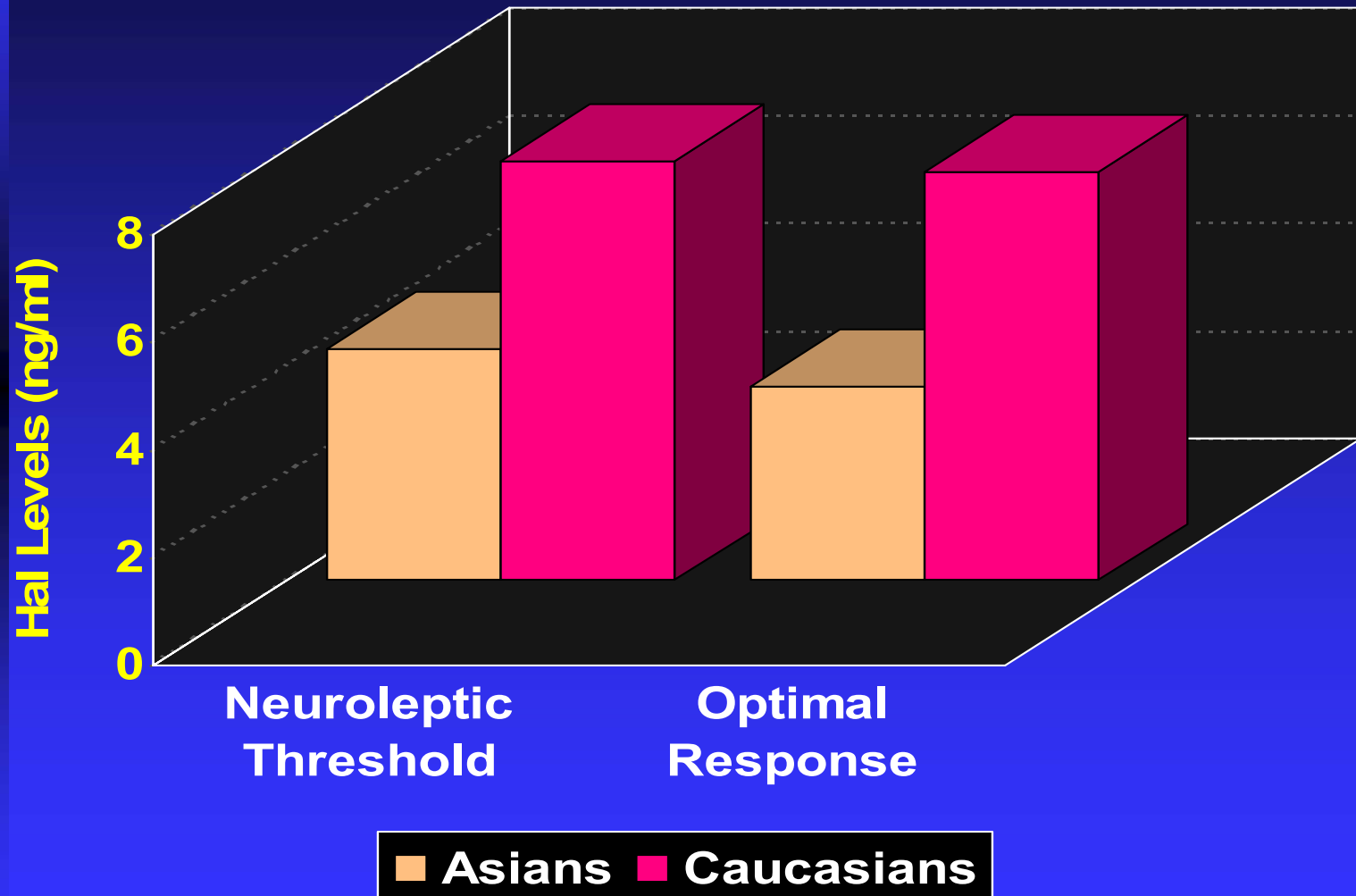


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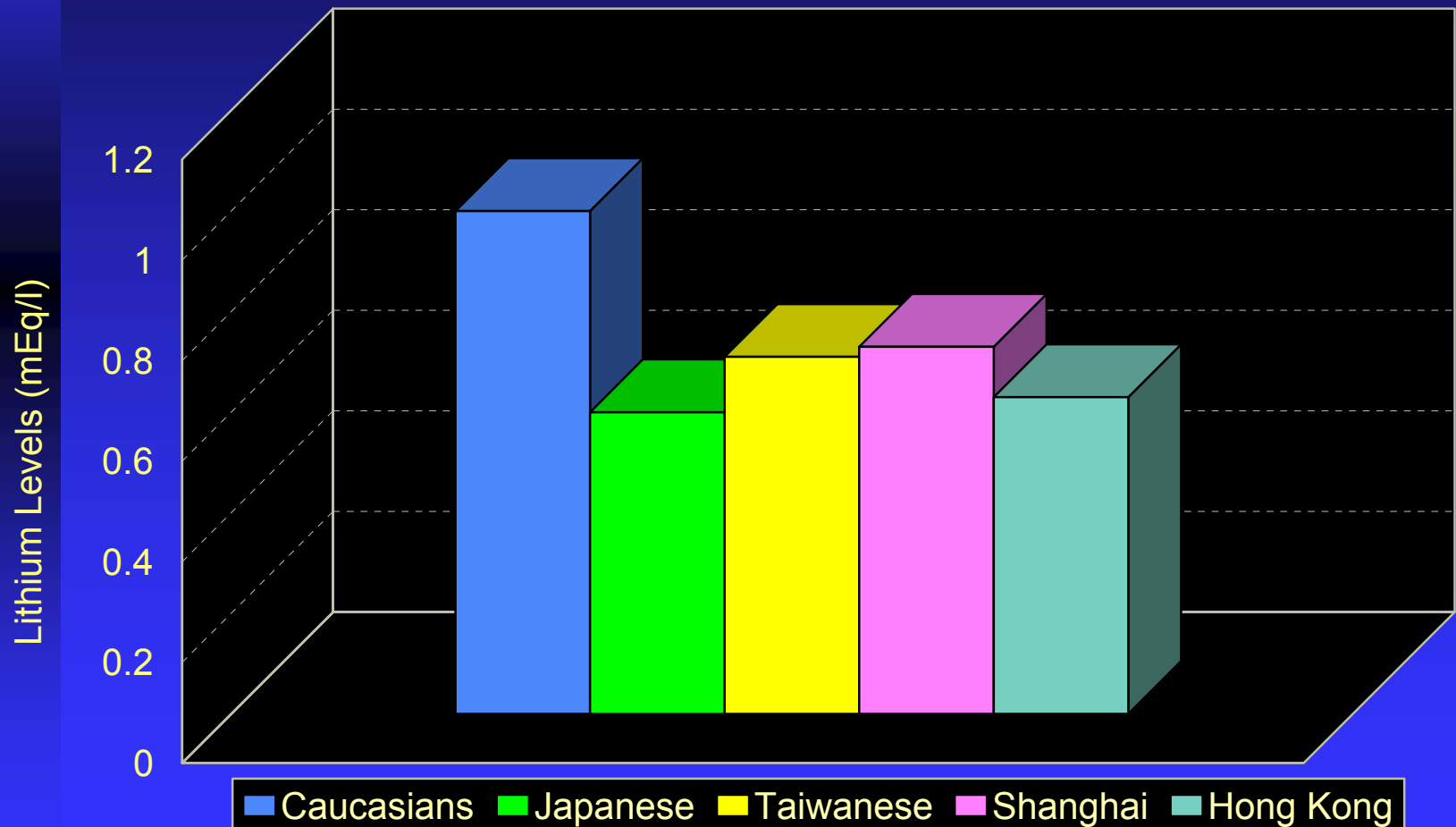
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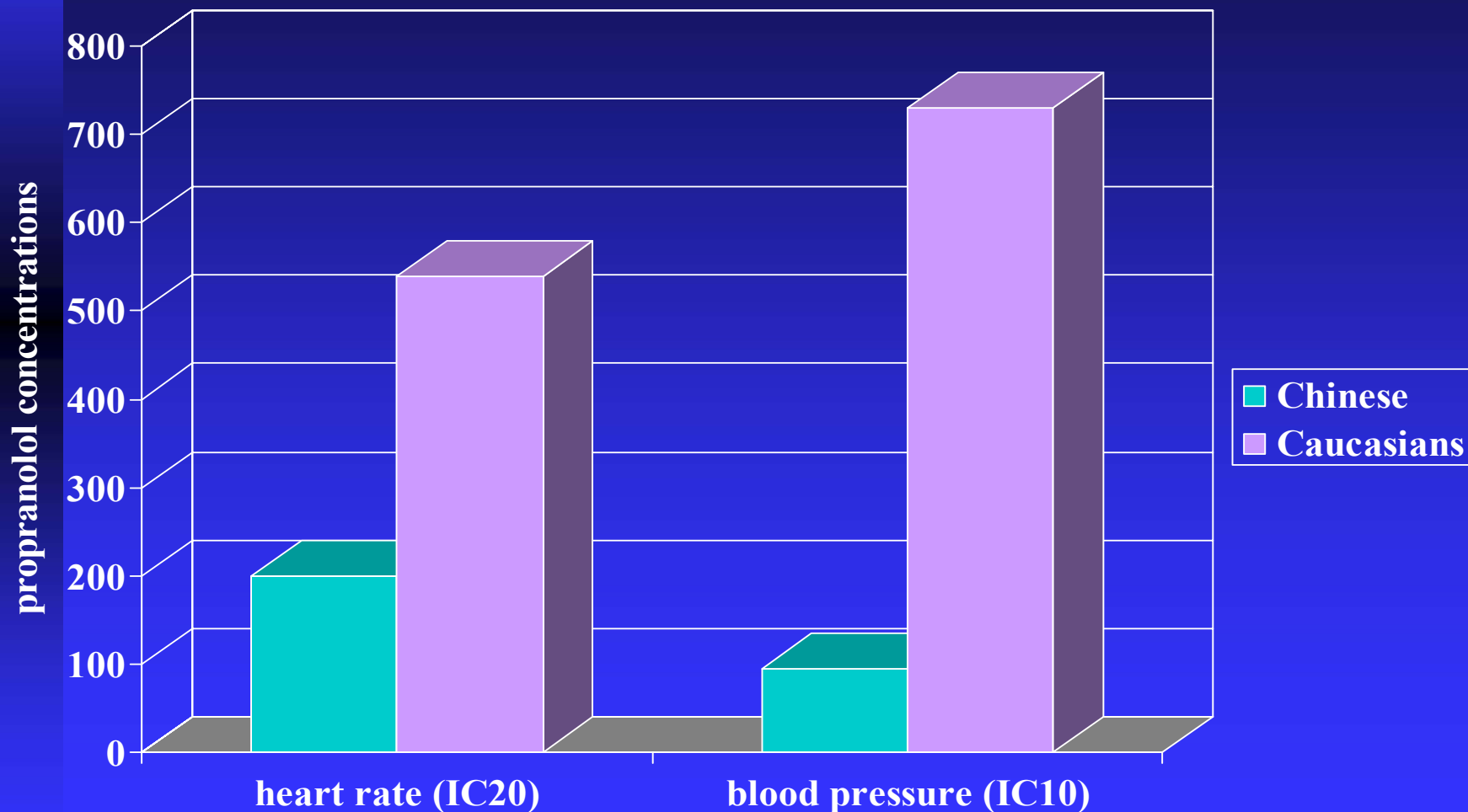
# Neuroleptic Dose and Level at the Neuroleptic Threshold and Optimal Response Points for Asian and Caucasian Patients



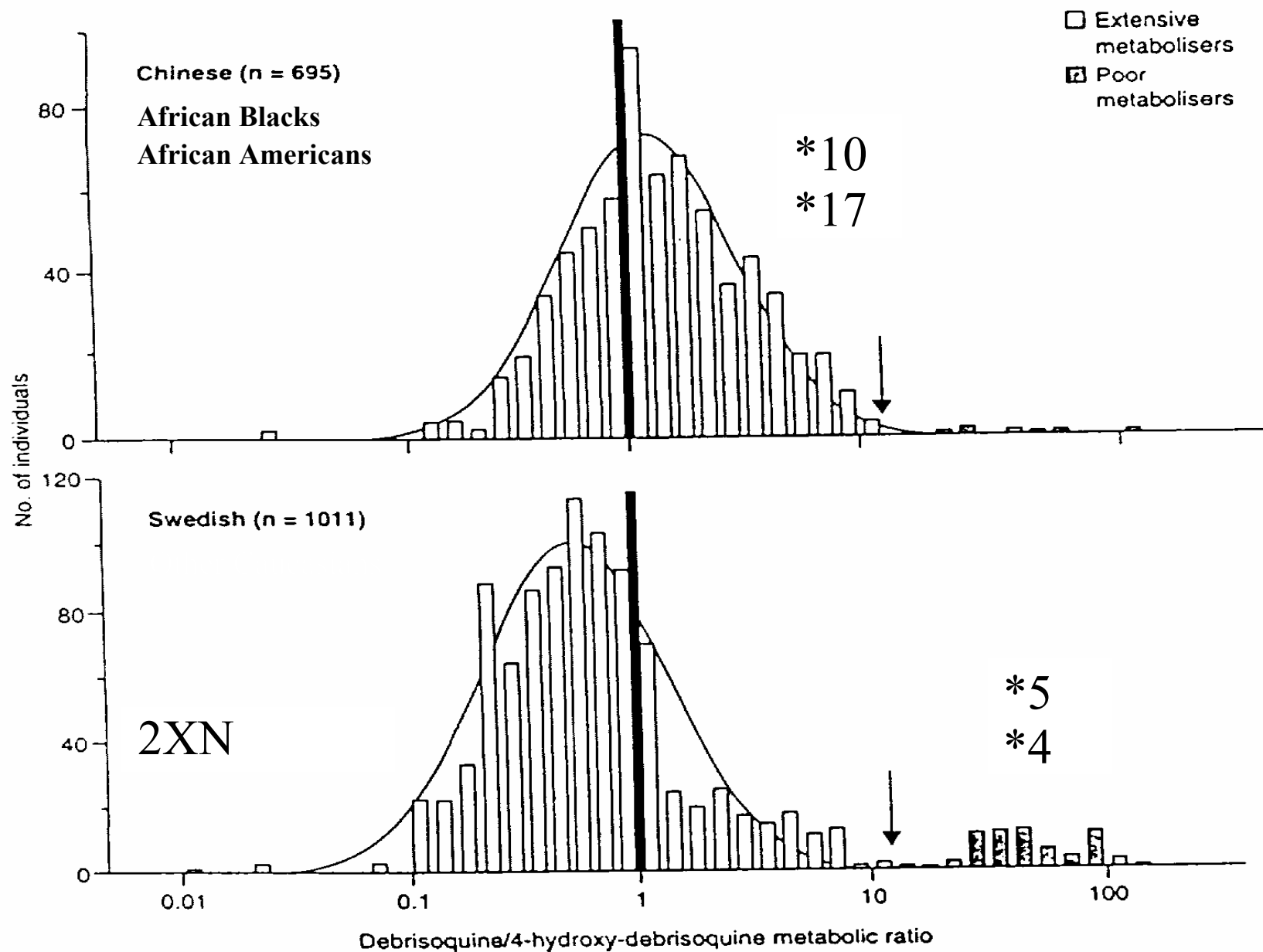
# Therapeutic Lithium Concentrations



# Propranolol Response: Chinese vs Caucasians



Zhou et al., NEJM 320:565-70, 1989



**Fig. 2.** Distribution of the urinary debrisoquine/4-hydroxy-debrisoquine metabolic ratio (MR) in 695 Chinese and 1011 Swedish Caucasian healthy individuals. The arrows indicate a MR of 12.6, the antimode between extensive metabolisers and poor metabolisers as established in Caucasian populations. A line is drawn at a MR of 1.0. Most Chinese extensive metabolisers have a MR > 1, while most Swedish extensive metabolisers have a MR < 1 (reproduced from Berilsson et al.,<sup>[14]</sup> with permission).